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Dynamics of Ventricular Contraction under Abnormal Conditions

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This lecture reviewed selected types of experiments carried out in our laboratory which are relevant to the interpretation of clinical disorders. From an analysis of ventricular pressure pulses, inferences were drawn as to basic determinants of cardiac performance in experimental conditions simulating those which arise clinically. The analysis included alterations in ventricular contraction patterns produced by pericardial effusion, hypervolemia, oligemia, arterial hypertension of peripheral origin and that due to coarctation of the aorta, aortic and pulmonary stenosis, idioventricular rhythms, ventricular alternation, coronary occlusion and myocardial ischemia, aortic regurgitation, and mitral insufficiency.

WITHIN the past two decades clinical and experimental studies of cardiac output—per minute and per beat—have yielded much important information concerning the nature of cardiovascular disorders. However, a basic understanding of such conditions also requires a comprehension of the ways and means by which cardiac output is either maintained or altered. The dynamics of ventricular contraction, which concerns itself with the mechanisms through which cardiac output is altered, can be evaluated to a considerable extent by a rigid analysis of pressure pulses recorded from the ventricular cavities.

Now it happens that during various periods since 1912 I have used such pressure pulses to study the basic changes in cardiac behavior produced during abnormal circulatory conditions in experimental animals. Since this work was published largely in journals of physiology previous to the awakening of clinical interest in cardiodynamics, much of it probably lies dormant on library shelves. In view of the current clinical interest, this lecture affords an appropriate occasion for recalling some of these studies and suggesting that experimental work of this nature be given consideration in the evaluation of human cardiovascular problems. It remains my considered judgment that deductions regarding cardiac behavior derived from controllable acute experiments on the dog's heart can be transferred to human hearts, provided that proper reserve and caution are exercised.

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THE INTERPRETATION OF VENTRICULAR PRESSURE PULSES

An investigator who attempts to draw conclusions from records of ventricular pressure pulses must exercise certain precautions if he wishes to avoid the formulation of wrong deductions. Recorded curves should always be examined and evaluated as to their reliability, that is to say, whether they truly depict pressure fluctuations or are distorted by artefacts of registration. The latter are more easily introduced than avoided. Distortion of ventricular pressure curves results from the use of inadequate manometer systems.[1, 2] Theoretic physical formulations and practical tests have

demonstrated that reliable curves can be recorded only by a manometer system which has an adequate frequency and proper damping characteristics expressed by the logarithmic decrement of its free vibrations. There have been and still are investigators who maintain that curves with high frequency components can be inscribed with properly damped low frequency manometers. Such a task appears to resemble one which would require a bass fiddle player to perform a musical score written for flute or piccolo.

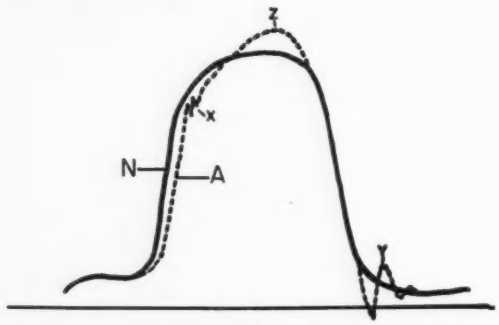

FIG. 1. Two graphs of a true left ventricular pressure pulse (N) and the same deformed through artefacts (A). In the latter the delayed rise, the superimposed vibrations (X), the dip and aftervibrations (Y) following relaxation are artefacts common to undamped low frequency systems. The late systolic rise (Z) which can generally be abolished by changing position of intracardiac sound is of uncertain origin.

Artefacts are also produced through periodic obstruction of manometer tubes or through displacement of a catheter and the heart in relation to one another during contraction and relaxation, but these are usually recognizable, and when present must be discounted. A few common distortions of ventricular pressure curves are shown in the assembly of records in figure 1. The heavy lined curve (N) represents the actual pressure fluctuations; the other curve (A) combines various distortions which may appear singly or in combination in records.

Ventricular pressure curves may display apparent rather than real differences in their patterns depending on the sensitivity of the manometers employed and the speed at which curves are recorded on moving paper. Thus, curve A in figure 2 is a typical normal curve. If the same pressure pulse is recorded by a manometer having twice the sensitivity, curve B emerges, and if this record be taken at half the paper speed, curve C develops. It is apparent that important inflections tend to be obscured in curve C and that artefacts might not be recognizable. If, in addition, the amplitude of such a curve is reduced to 1.0 cm. by use of direct recorders, contour changes cannot be inferred. A judicious balance between ordinate

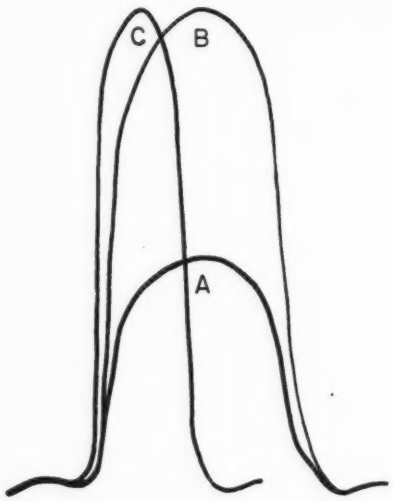

FIG. 2. Identical ventricular pressure pulses recorded with manometers of different sensitivity (A, B) and on paper traveling at different speeds (B, C).

and abscissal values is obviously important in the registration of pressure pulses.

A proper interpretation of myocardial activity through analysis of the ventricular pressure pulse requires a knowledge of its relationship to other cardiodynamic events. The relation of ventricular pressure variations during successive phases of the heart cycle to pressure changes in the aorta and left atrium, to a surface myogram, to acoustic phenomena, to volume changes of the ventricles, and to an electrocardiogram (standard lead II) are shown in figure 3. The persistence with which curves of inaccurate contours and erroneous time relations continue to appear in papers and textbooks makes publication of such a chart de-

sirable. A comprehension of correlated events expressed in such a series of curves was once regarded as an academic exercise; in the current era of hemodynamic studies it becomes an inescapable requirement.

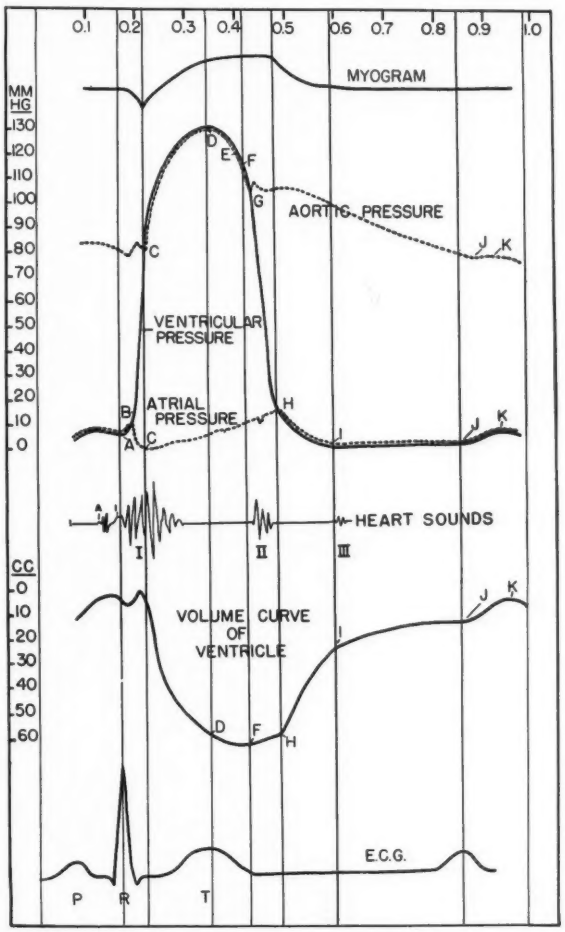

FIG. 3. Chart showing correlation of various dynamic, mechanical, acoustic, and electrical events during a cardiac cycle.

SUCCESSIVE MYOCARDIAL AND DYNAMIC EVENTS DURING THE CARDIAC CYCLE

The subdivision of the cardiac cycle which I[3] suggested in 1921 has apparently gained rather general acceptance. According to this scheme, mechanical systole begins with the rise of pressure at A and ends with the release of tension in all muscle units at F (fig. 3). It is divided into phases of *isometric contraction* (A–C), *maximum ejection* (C–D) and *reduced ejection* (D–F). The subsequent period of diastole is divided into phases of *protodiastole*, representing the time required for closure of the *semilunar valves* (F–G), *isometric relaxation* (G–H), *rapid ventricular filling* (H–I), *diastasis* (I–J), and filling by *atrial contraction* (J–K).

Abnormal patterns of ventricular contraction cannot be inferred from ventricular pressure pulses unless an investigator or reader possesses the capacity for translating the tracings into

mental pictures of processes which take place in the heart and vascular system during the period of the heart cycle outlined by the ventricular pressure curve. We may therefore review briefly the main muscular and hemodynamic events which are associated with the phases of isometric contraction, systolic ejection, and isometric relaxation. As a prelude to such discussion, the dynamic effort of the heart during these respective phases may be compared to the task of (1) raising a pail of water from the ground to a high level, (2) holding it at this level while most of its contents are thrown with some force over a wall, and (3) bringing the pail back to the ground for refilling.

At the onset of mechanical systole at A the entire myocardium of the left ventricle has been excited. This is evidenced by its coincidence with the peak of R of a standard or direct electrocardiographic lead.[4, 5] Owing to a latency, however, only the initially excited fractions have started to contract. As more and more contractile fractions summate, the pressure rises slowly at first (A–B), but very rapidly as soon as all fractions participate in the summation process (B–C). Since the mitral and semilunar valves are closed during the interval A–C and blood neither enters nor leaves the left ventricle, contraction is essentially isometric, that is, energy of contraction is converted to tension. Actually, however, a little energy is lost through a slight yielding of the valvular structures and in readjustments in the form and position of the heart. In the development of a rigid muscular state, the ventricles rotate, assume a more globular shape, and exert a traction on the atria and large vessels. Myograms recorded from the left ventricular surface, such as are reproduced in figure 3, reveal that the surface layers may even lengthen as a result of changes in form of the ventricle. However, reduction in the base to apex axis demonstrates that the septal fibers undergo a shortening. This afterloaded mode of ventricular contraction has the advantage that sufficient vis a tergo is developed to start quickly and continue a brusque and forceful ejection of blood into the aorta against a relatively high aortic resistance.

The ejection of blood takes place within a relatively short period (C–F); it is about 0.25 second in man and less in lower animals. Reference to volume curves of the ventricles (fig. 3) reveals that two-thirds of the whole stroke volume is ejected during the first half of this period (C–D) and a comparatively small fraction during the latter half (D–F). Since efflux of blood from aortic branches exceeds uptake from the ventricles during the latter half of ejection, the pressures in the aorta and left ventricle decline (D–F). Thus the summits of the ventricular and aortic pressures demarcate the transition from rapid to reduced systolic ejection. More than this, the inflections of the

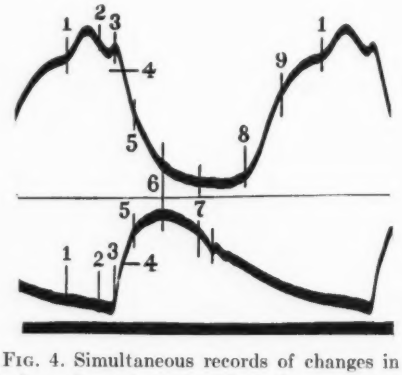

FIG. 4. Simultaneous records of changes in ventricular volume (upper) and aortic pressure (lower) demonstrating the correspondence of inflections (1–7) during systolic ejection. Volume curve is inscribed so that emptying of ventricles is recorded as downstroke, filling as upstroke.

ventricular as well as of the aortic pressure curves from C to F reflect minor changes in the rate of systolic ejection. This is clearly illustrated by comparing changes in ventricular volume with pressure variations in the root of the aorta in figure 4. The initial steep rise of aortic pressure (3–4) is accompanied by a brusque movement of only a small volume of blood into the aorta. The continued elevation of aortic pressure from 4 to 5 is attended by a rapid emptying of the ventricle. During the slower rise of aortic pressure to a summit (5–6) the rate of ventricular emptying diminishes progressively, and during the systolic decline of pressure (6–7) it is very low. It is apparent that, despite the variable efflux from the aorta, the configuration of the aortic (and ventricular)

pressure pulses is dominated by the changing rates of ventricular emptying.

From a dynamic standpoint, mechanical systole terminates at F (fig. 3), for all muscle fractions have ceased to develop tension.[3] The completion of the T deflection by this time indicates that repolarization has been completed.[4] However, theoretic considerations[6] and the responses to electrical stimuli[7] strongly favor the view that some fibers have ceased to develop tension earlier, for example at E. This does not mean that a lengthening of myocardial fibers has commenced. On the contrary, myograms

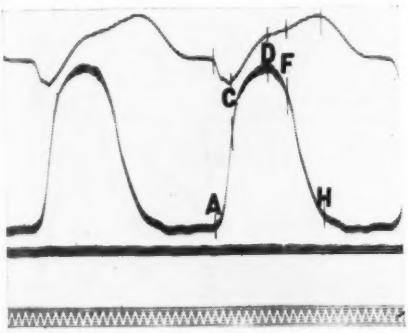

FIG. 5. Simultaneous records of the changes in length of a small area of the left ventricular surface (upper curve) related to a ventricular pressure pulse (lower curve). A-C, isometric contraction; C-D, maximal systolic ejection; D-F, reduced ejection and protodiastole; F-H, isometric relaxation. Note that shortening of surface fibers begins at C and terminates at H. Time, .02 second.

reproduced in figures 3 and 5 demonstrate that the ventricular relaxation starts with a reduction of tension for .08 second or longer (G–H) before the fibers lengthen (H–I) and ventricular filling begins.[8] It has been tempting to relate the gradient of pressure decline and the duration of the isometric relaxation phases (G–H) to physiologic differences in the relaxation process. However, physical forces cannot be wholly excluded. These include effects of (1) the coronary refilling, (2) the volume of residual blood remaining after ejection, (3) the pressure at the onset of isometric relaxation, and (4) the atrial pressure which determines the time at which curves intercept at H. It may be added, however, that myograms such as are reproduced in figure 5 offer no support for the view that refilling of the coronary vessels during isometric relaxation stretches the myocardium.

Determinants of Myocardial Responses

The contraction pattern of the ventricles is determined by factors that affect the physiologic condition of the heart muscle directly and by those that act through changes in input and output loads. The former have been termed primary and the latter secondary coefficients.[9, 10] Primary coefficients include the direct myocardial effects of local metabolites, fatigue, abnormal chemical constituents of the blood including drugs, coronary insufficiency, and nervous impulses. Through these true cardiac stimulation or depression is produced. Secondary coefficients cause alterations in cardiac output by modifying the diastolic filling or arterial resistance. In pathologic conditions, tertiary coefficients can significantly modify the ventricular contraction patterns in mechanical ways. These include such factors as an abnormal sequence or deletion of fractionate contractions and valvular lesions which cause the ventricles to contract in a loaded or isometric rather than an afterloaded manner.

As Starling and his associates[11] inferred from studies on a heart-lung preparation, the responses of a ventricle under many normal and pathologic conditions are determined by its presystolic size or the initial length from which fibers start their contraction. Personal experience[1, 10] has confirmed Frank's earlier postulate that, with exceptions to be noted later, changes in initial length are produced by alterations in ventricular pressure at the onset of contraction, namely, by the initial tension. Such changes though small are usually discernible in optical records of sufficient amplitude. However, controlled conditions are required for studying the effects of such a secondary coefficient. These conditions are that the heart rate remains constant and that the myocardial reactions are not simultaneously affected by primary or tertiary factors enumerated above.

Basic studies on controlled circulation experiments[10]—in which a constant heart rate is maintained and venous inflow and arterial resistance can be adjusted independently—have revealed

that alterations in the pattern of ventricular contractions produced by primary and secondary coefficients can be distinguished by the relation that the amplitude, form, and duration of contractions bear to initial tension. Thus, as illustrated by curves 1 and 2 of figure 6 *I*, progressive elevations of initial tension at A are accompanied by increasing force and duration of contractions up to a critical level. When a critical degree of stretch is exceeded, initial tension increases more rapidly and is followed by contractions having a more gradual rise, a lower amplitude, and a shorter duration, as depicted in curve 3 of figure 6 *I*. These changes from a normal curve N illustrate compensation and decompensation with increasing input loads. It may be added that the decompensatory responses must probably be assigned to some innate effect on the myocardium, perhaps a fatigue process. The effects of primary coefficients are illustrated by the curves of figure 6 *II*. If the myocardium is stimulated, as by epinephrine or accelerator nervous impulses, while heart rate and venous return are kept constant, the contractions become larger, steeper, and shorter in duration; the stroke volumes increase, and consequently the initial tension declines. Such a response is shown in curve 1. If, on the contrary, the ventricular muscle is depressed, as by chloral hydrate or Pitressin, the ventricular contractions become more gradual, reach a lower summit and are abbreviated; the stroke volume is reduced, and initial tension is elevated through development of a larger reserve volume.

From these observations the rule can be de-

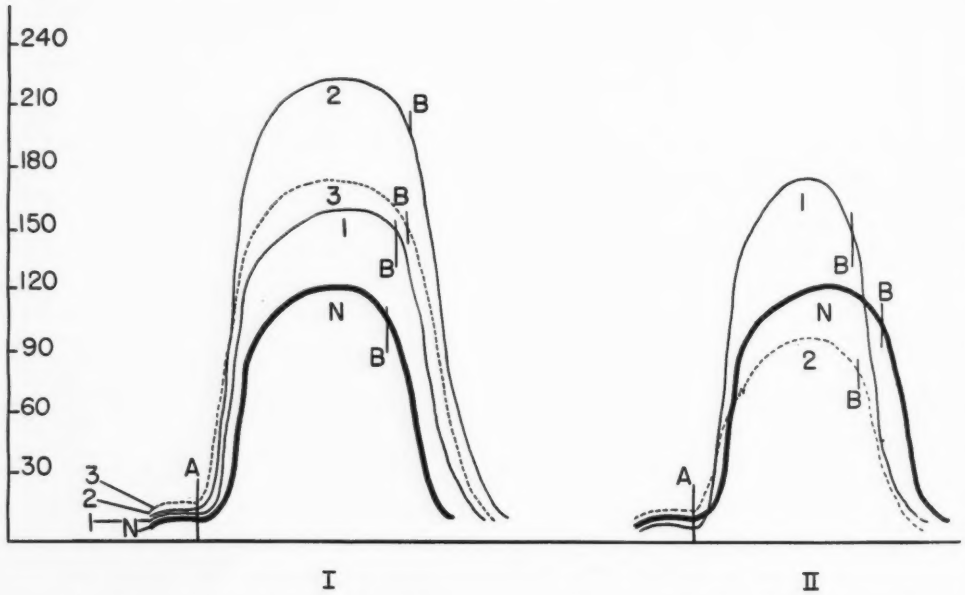

FIG. 6. Assemblies of transcribed ventricular pressure pulses comparing the effect of progressive increase in initial length and tension (secondary coefficients) and the effects of primary myocardial coefficients.

I. N, normal curve; 1, 2, compensatory responses to increasing initial tension following rapid saline infusion; 3, decompensating response from overdistention by a large infusion. Note progressive increase in initial tension at A and lengthening of systole, A-B.

II. N, normal curve; 1, augmentation of contraction with fall in initial tension (A) and shortening of systole (A-B) following a dose of epinephrine in a preparation with controlled heart rate; 2, depression of contraction with elevation of initial tension, slower gradient, and abbreviation of contraction (A-B) following a small dose of chloral hydrate, heart rate controlled.

duced (1) that secondary changes in ventricular response can be inferred from ventricular pressure curves when initial tension and amplitude of contraction alter in the same direction, and (2) that primary changes in ventricular response are characterized by opposite changes in initial tension and amplitude of contraction. It must be recognized of course that in the body primary and secondary factors frequently operate at the same time. Thus, even when tertiary factors are not involved, it often becomes difficult, if not impossible, to determine the basic mechanisms which govern ventricular performance. It was again emphasized recently[10] that such a dilemma arises when comparative observations are made at differing heart rates, for the duration of diastolic filling affects initial tension and length and therefore the magnitude, vigor, and duration of ventricular contractions. The advantages of studying the mechanism of abnormal cardiac responses in experimental animals in which heart rate as well as input and output loads are controllable, rather than in human subjects in whom this cannot be achieved, should be obvious.

With this brief orientation we shall proceed to analyze the mechanisms which determine ventricular contraction patterns in a number of experimental conditions which simulate clinical circulatory disorders.

Pericardial Effusion

The dynamic changes produced by degrees of pericardial effusion which significantly interfere with ventricular filling and thereby cause reduction in cardiac output have been thoroughly worked out by a number of investigators.[12-15] Our discussion is advisedly limited to a consideration of the support that studies on pericardial effusion have given to the thesis that change in initial length rather than initial tension is the basic secondary determinant of ventricular response.

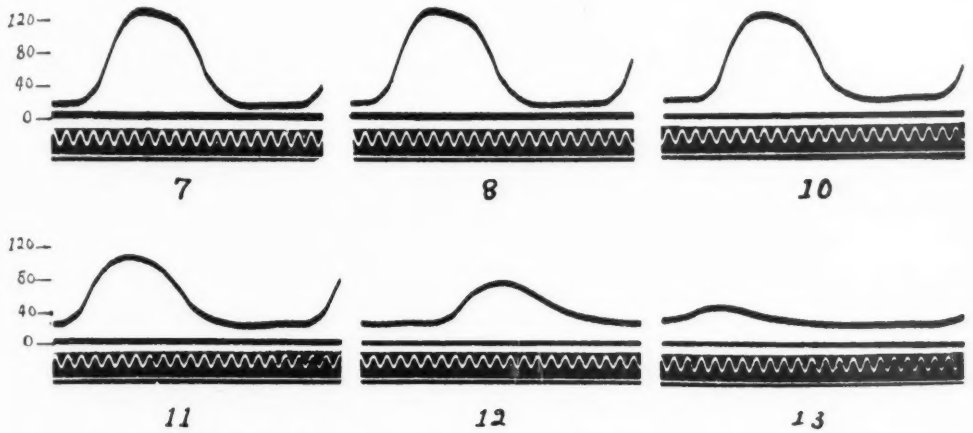

FIG. 7. Series of left ventricular pressure curves, showing how progressive increases in pericardial fluid and pressure steadily elevate initial tension in relation to a base line, but decrease maximal ventricular pressures and gradients of contraction. Pericardial pressures expressed in mm. Hg as follows: Curve 7 = 15 mm.; 8 = 75 mm.; 10 = 90 mm.; 11 = 100 mm.; 12 = 135 mm.; 13, very high, reading doubtful.

Since initial tension and length generally alter in the same direction, it has proved difficult to draw inferences as to which of the variables basically affects myocardial response. The deduction of Starling and his associates[11] that the energy of contraction, however measured, is determined by changes in initial length of the muscle fibers has been since confirmed by numerous studies in which a dissociation of initial length and tension was achieved by experimental expedients. (For bibliography see reference 10.)

When the volume of liquid within the peri-

cardium exceeds the natural available space, the intrapericardial structures are compressed by increasing pressure around them.[15] The initial tension within the ventricles rises almost proportionally, but their diastolic size decreases owing to the impairment of filling. The fact that changes in initial tension and length are dissociated thus afforded me an opportunity to determine experimentally which of these factors dominates cardiac response.[16] Some of the changes found in ventricular pressure pulses are illustrated by records of figure 7. Each increase in pericardial and initial ventricular tension is accompanied by development of less pressure and slower gradients. The durations of isometric contraction and ejection decrease despite some lengthening of the heart cycle. All of these reactions are obviously the opposite of those normally associated with increase in initial tension, whereas they accord with changes resulting from reduction in presystolic size or initial length of myocardial fibers.

Hypervolemia

The basic reactions which accompany an increase in plasma volume can be reduplicated experimentally by venous infusions of saline solutions or serum. Briefly recapitulated, the following chain of events takes place: the greater output of the right ventricle not only elevates left atrial pressure at the moment when the mitral valves open but also induces more vigorous atrial systoles. Through these two mechanisms the left ventricle is more completely filled, and initial tension is elevated. The ventricular responses are those exemplified by curves I and II of figure 6. Characteristic effects consist of a steeper isometric gradient, quicker rise of pressure to a higher peak during ejection, and a prolongation of systole. The larger stroke volume which accompanies these pressure changes is achieved through the combined effects of a higher velocity of ejection and prolongation of the ejection phase.[17]

Acute production of polycythemic hypervolemia evokes similar responses. Figure 8 shows representative curves recorded by Gregg and myself[18] after injection of sedimented matched corpuscles over a period of five minutes. Comparison of curves *A* and *B* reveals an elevation of initial tension, a steeper isometric gradient, a higher systolic pressure, and an extension of systole. All are typical changes induced by concordant increases in initial tension and length. The effects persist for a considerable time, as shown in curves *C* and *D* recorded respectively 80 and 115 minutes after the infusion of erythrocytes had ceased. An analysis of aortic pressure pulses led to the conclusion that the augmented peripheral resistance occasioned by greater viscosity of the blood and the strain of a higher input load were less important determinants of left ventricular response. However, it may be noted in these records that, whereas systole is somewhat prolonged in

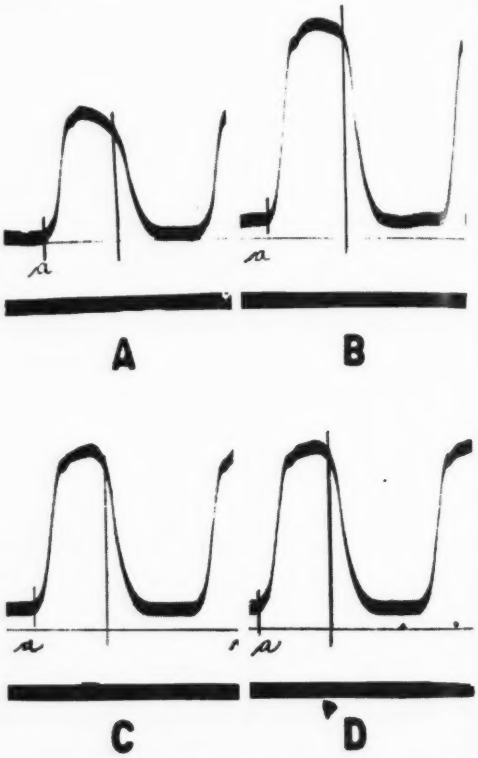

Fig. 8. Four left ventricular pressure curves: *A*, control; *B*, shortly after infusion of 200 cc. sedimented matched corpuscles in 5 min.; *C*, 80 minutes later; *D*, 115 min. later. Observe elevation of initial tension at *a* and higher pressure maxima. Durations of systole as follows in seconds: *A*, 0.172; *B*, 0.185; *C*, 0.170; *D*, 0.172.

curve *B*, it shortens again in curves *C* and *D*, suggesting an influence of the higher output load (see later).

Oligemia

Reduction in blood volume, such as exists after a severe hemorrhage, has reversed effects on ventricular pressure curves. However, if a state of hypotension is maintained for long intervals, the myocardium is depressed presumably through defective coronary flow. As a result, the ventricles expel smaller stroke volumes; their residual volume becomes larger, and initial tension returns to normal levels.

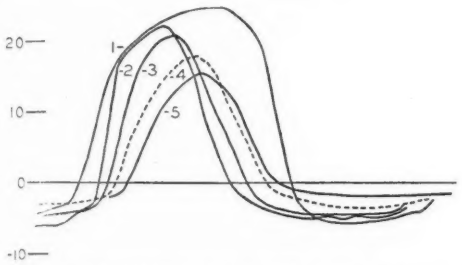

Fig. 9. Assemblage of transcribed curves showing pressure changes in the right ventricle after hemorrhage and transfusion. Discussion in text. (After Opdyke and Wiggers[19])

Since pressure and resistance decline less in the pulmonary artery than in the aorta, the basic effects of prolonged diminution in venous return are exhibited better in the right heart. Some changes in right ventricular behavior reported by Opdyke and myself[19] are reproduced in figure 9. Curve 1 represents a right ventricular pressure curve taken as a control. Curve 2 was recorded shortly after arterial mean pressure had been reduced to 65 mm. Hg by a severe hemorrhage. The isometric ascent remains steep despite a fall in initial tension, but systole is typically abridged, and the systolic summit is lower. Curve 3 was recorded after a state of hypotension at a 50 mm. Hg level had persisted for 88 minutes. The slower rise of pressure to a lower summit and a further abbreviation of systole regardless of the slight recovery of initial tension are obvious. Curve 4 was recorded immediately after a further reduction of arterial pressure to 30 mm. Hg and curve 5, 45 minutes later. Initial tension is elevated above that of the control curve 1, but the gradients and summits of the pressure curves are decidedly reduced. Such deterioration of contraction with rising initial tension strongly suggests that a primary myocardial depression has supervened. (For further work see reference 2.)

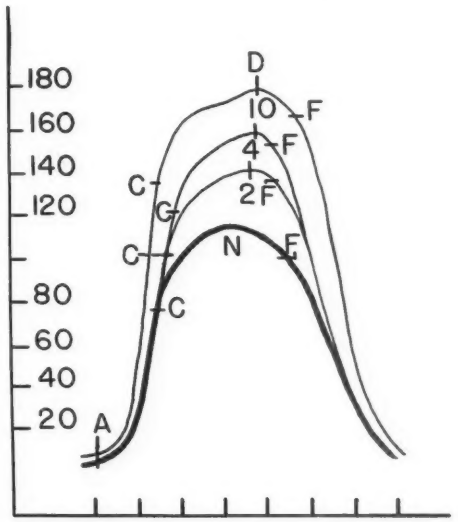

Fig. 10. Assemblage of transcribed curves indicating changes in left ventricular pressure from normal (N) during the second, fourth, and tenth beats after sudden compression of the aorta just above the diaphragm. In beats 2 and 4 note same initial tension, prolongation of isometric contraction (A-C), displacement of summit (D) later in systole, and earlier termination of systole at F. In beat 10 note additional effects of increasing initial tension at A, such as steeper isometric gradient, higher systolic pressure (D), and prolongation of systole (A-F).

Arterial Hypertension of Peripheral Origin

The effects of increased peripheral resistance on ventricular contraction patterns can be analyzed best by applying a mechanical constrictor to the aorta just above the diaphragm.[1, 20] Even so, adaptation occurs in two stages. The first stage, illustrated by curves labeled 2 and 4 in figure 10, persists only for the first two to five beats after a sudden constriction. The changes in the ventricular pressure pulses are solely attributable to increased aortic resistance, for the initial

tension remains unaltered. Since ventricular pressure must be elevated to higher levels before the semilunar valves open, isometric contraction (A–C) is slightly prolonged. The isometric pressure gradient is not affected, because the ventricle is not exposed to the higher aortic pressure during this period.

In response to a higher aortic pressure, the systolic ejection period (C–F) is typically abridged[17] and to such an extent that systole as a whole (A–F) is also shorter. The pressure rises to a higher summit (D). These immediate reactions are important in demonstrating that the basic response to a sudden increase in aortic resistance consists in development of greater tension with abbreviation of contraction. However, with each contraction, the stroke volume is not quite normal; a small amount of blood is retained and, with a normal inflow volume, quickly increases the presystolic size and initial tension. The second stage then supervenes.

Curve 10 of figure 10 illustrates these secondary effects in the tenth beat following aortic compression. Initial tension is slightly elevated, the isometric gradient is steeper, the period of isometric contraction decreases, and the ejection phase C–F is prolonged. The reactions of the ventricle to increased initial tension and length obviously become dominant. Changes in the contour of the pressure summits reveal that the pattern of systolic ejection has changed. The continued elevation of pressure nearly to the end of systole indicates that the rate of ejection is more sustained than under normal conditions.

Responses of a similar nature follow generalized augmentation of arteriolar resistance, such as can be induced by stimulating the central ends of the vagus nerves. The myocardial responses are complicated, however, by the greater venous return which follows displacement of blood from minute peripheral vessels and the spleen and by augmentation of coronary flow. Consequently the output of the right heart quickly increases and larger volumes of blood are delivered to the left heart.[21] The rise of initial pressure and the left ventricular responses are thus accentuated to such an extent that the stroke volume actually exceeds the normal.

Aortic Coarctation

Clinical types of aortic coarctation can be simulated by stepwise constriction of the aorta proximal to the left subclavian artery. Recent studies by Gupta and myself[22] have shown that the lumen of the aorta must be reduced by 55 to 60 per cent before an elevation of aortic and left ventricular pressures ensues. Figure 11 shows some consequences of effective degrees of

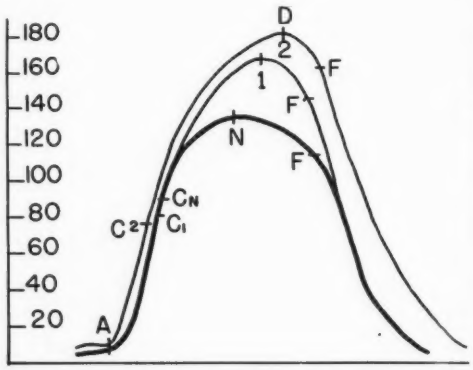

Fig. 11. Assemblage of transcribed records showing deviations from a normal left ventricular pressure curve (N) following reduction in aortic lumen just peripheral to subclavian artery, by 60 per cent in curve 1, and by 87 per cent in curve 2. Note abbreviation of the isometric phase (A-C), the delayed summit (D), and the abbreviation of contraction (A-F), curve 1. Also observe the higher initial tension (A) the higher rounded summit (D) and lengthening of systole (A-F) in curve 2.

coarctation. Comparison of these curves with those of figure 10 reveals many similarities, but there are two important differences. In the former aortic diastolic pressure rises; in the latter it declines. Consequently, in coarctation isometric contraction is terminated earlier, as indicated at C_1 and C_2 on curves of figure 11. Also initial tension (A) fails to increase until the aorta has been constricted to 80 per cent of its natural diameter. As soon as initial tension increases, systolic ventricular pressure is elevated still more, as shown in curve 2 of figure 11, and the systolic discharge also becomes greater.

Since augmented stroke volumes are realized despite a marked reduction in aortic pressure below the coarctation, and hence a drastic decrease in inferior caval flow, the inference follows that total venous return is rebalanced through corresponding augmentation in superior caval and coronary flows. The correctness of this deduction had been previously demonstrated in similar experiments, performed in conjunction with Katz,[21] which indicated that right atrial and ventricular pressures may even elevate slightly, owing to a somewhat greater total venous return.

It has been emphasized[22] that the augmented pulse pressure central to a coarctation is associated with a decline of diastolic pressure. Such hemodynamic effects cannot be attributed to an increase in aortic resistance at the site of narrowing or to an augmented stroke volume. It became obvious to us,[22] however, that, when an effective constriction exists, the capacity of the aortic compression chamber becomes very small, and its volume elasticity coefficient (dP/dV) is greatly increased. Now it can be demonstrated on artificial circulation models[23, 24] that, when equivalent stroke volumes need to be taken up in a compression chamber which is less distensible (increase in dP/dV), the mean pressure alters very little, but systolic pressure rises and diastolic pressure falls. Hence Gupta and I[22] concluded that the central effects of aortic coarctation are not wholly due to increased resistance at the locus of coarctation, but that they also involve reduction in capacity and distensibility of the compression chamber. The latter is wholly responsible for the reduction of diastolic pressure and contributes to the elevation of systolic pressure in the aorta and left ventricle.

Aortic Stenosis

This pathologic condition is usually studied experimentally by tightening a cord around the aorta in close proximity to the aortic orifice. Such a stenosis differs physically from that presented by coarctation in that the aortic compression chamber is entirely abolished and circulatory channels proximal to the stenosis return less blood to the right heart. All investigators agree that, as in the case of aortic coarctation, the aortic orifice must be narrowed to between 60 and 70 per cent of its original diameter before cardiac output per beat or per minute is reduced. (For bibliography see reference 25.) Nevertheless, narrowing of 15 to 30 per cent suffices to create audible and recordable murmurs.

The changes in left ventricular contraction depend on the degree of aortic narrowing. In

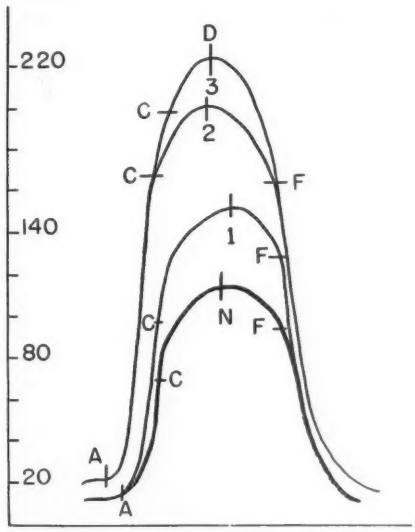

FIG. 12. Transcribed left ventricular pressure curves showing effects of different degrees of aortic stenosis. N, normal; curve 1 = 22 per cent constriction; curve 2 = 45 per cent constriction; curve 3 = 85 per cent constriction. Lettering as in previous figures. Description in text.

mild degrees of stenosis exemplified by curve 1 of figure 12 the ventricular pressure curves resemble those produced by moderate augmentation of aortic resistance shown in figure 10; initial tension and the isometric pressure gradient remain unaltered, but the pressure summit is higher and displaced to a later moment of systole. Isometric contraction (A–C) is prolonged slightly, but the duration of total systole (A–D) is not affected. De Heer,[26] who recorded similar curves, believed that such reactions typify the effects of aortic stenosis; augmentation of aortic resistance was considered to be the

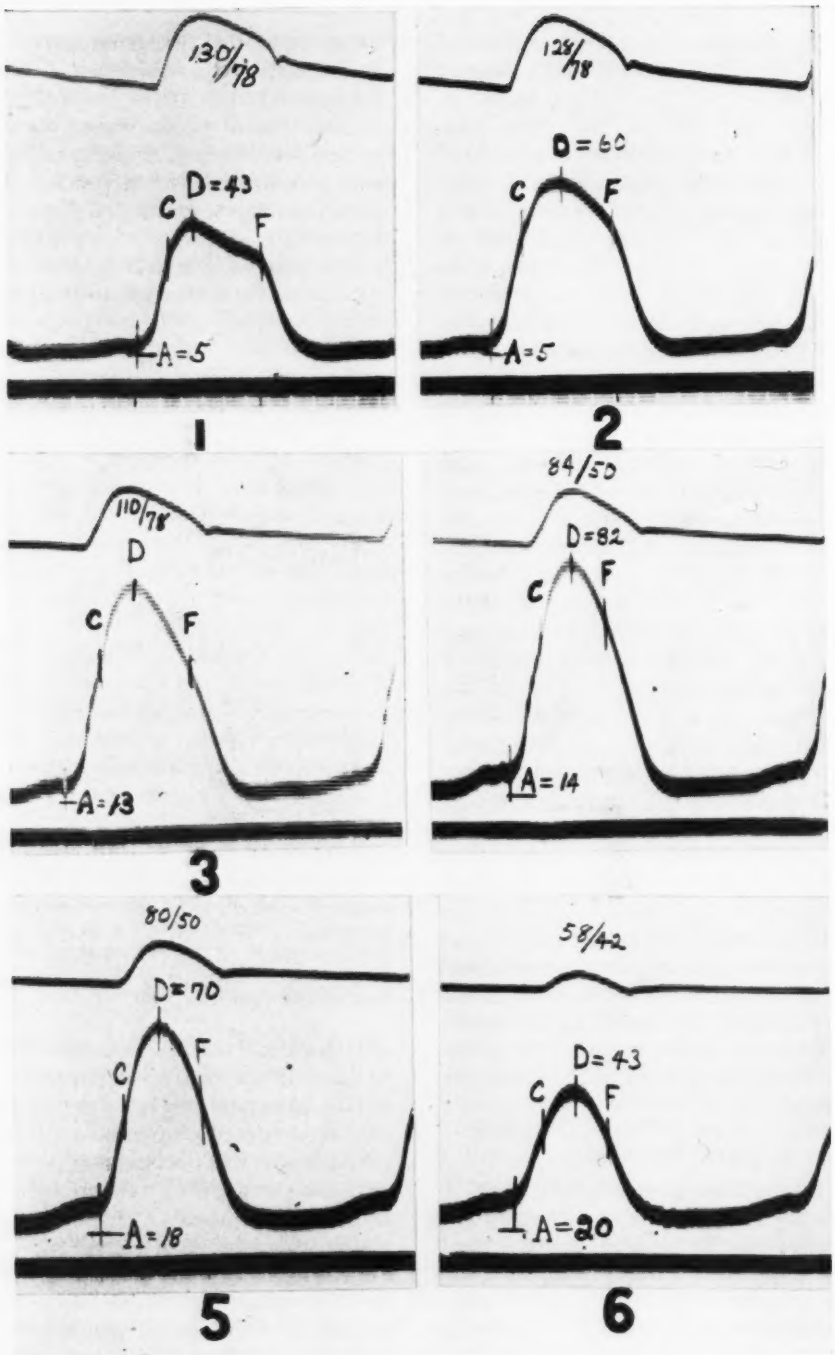

FIG. 13. Segments of records showing changes in aortic pressure (upper) and right ventricular pressures (lower) following stepwise increases of pulmonary stenosis. 1, control; 2 = 39 per cent constriction; 3 = 52 per cent constriction; 4 = 56 per cent constriction; 5 = 59 per cent constriction; 6 = 63 per cent constriction. Discussion in text.

chief determinant of myocardial response. However, Katz and his associates[27] found that the ventricular pressure curves are more peaked as soon as the degree of stenosis becomes dynamically significant. The pressure summit is reached earlier, not later, in systole. Such contraction patterns are shown in the transcribed curves 2 and 3 of figure 11. When ventricular ejection is seriously impeded, the ventricles approach an isometric type of contraction in which the increased residual volume and marked elevation of initial tension contribute to the production of very high systolic ventricular pressure.

It should be kept in mind that the reactions of the left ventricle may be more favorable in experimental than in clinical stenosis. In the former the constriction is peripheral to the coronary orifices, and coronary blood flow is decidedly enhanced; in the latter, the narrowing is proximal to the coronary ostia, and coronary flow is unquestionably reduced. In order to determine whether superposition of coronary insufficiency alters the mechanism of ventricular response, the effects of severe pulmonary stenosis may be analyzed.

Pulmonary Stenosis

Figure 13 contains six segments of records obtained by Fineberg and myself[28] during progressive circular compression of the pulmonary artery. Segments *1* to *3* show steady increases in initial tension, higher systolic summits, and contours similar to those observed in progressive aortic stenosis. It may be noted that the aortic pressures just begin to be affected in segment *3*, in which a 52 per cent reduction in the lumen of the pulmonary artery had been produced. A slightly greater constriction initiates a greater decline of arterial pressure, as shown by segments *4*, *5*, and *6* which respectively represent constrictions of 56, 59, and 63 per cent of the lumen. The right ventricular pressure curves all display contours typical of an isometric mode of contraction. However, as shown in segments *5* and *6*, the systolic summit rapidly falls with increasing stenosis instead of rising further, as in aortic stenosis (fig. 12). Since such decline of pressure is associated with marked elevation of initial tension, it is a logical inference that myocardial depression due to inadequate coronary flow has supervened.

Summarizing, the ability of the right or left ventricle to overcome the resistance of a narrowed aortic orifice depends as much upon the ability of the myocardium to compensate as upon the actual degree of narrowing. The responsiveness of the myocardium in turn depends on the adequacy or insufficiency of coronary blood flow.

The abnormalities of ventricular contraction so far considered illustrate conditions in which primary and secondary factors, separately or together, determine the nature of ventricular responses. We turn now to consideration of a few conditions in which tertiary factors play important roles.

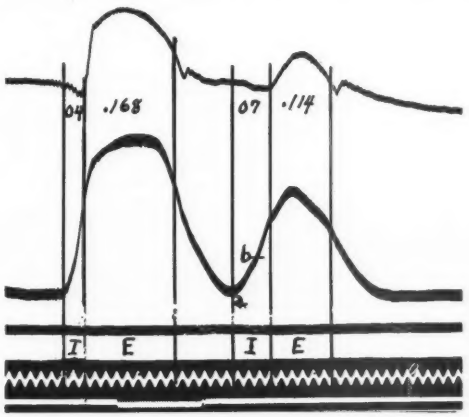

Fig. 14. Aortic (upper) and left ventricular (lower) curves depicting changes during an effective premature contraction. *I*, isometric phase; *E*, ejection phase. Time, .02 second. Discussion in text.

Idioventricular Rhythms

It is well established that premature ventricular contractions or a succession of such beats during ventricular tachycardia are characterized by delivery of smaller stroke volumes. The contraction patterns of a normal and a premature ventricular systole can be compared in the ventricular pressure curves shown in figure 14. The premature beat differs from the preceding normal one in several ways, namely the lower systolic pressure summit, the

changes in contour, the prolongation of isometric contraction (I), and the abbreviation of the ejection period (E) sufficient to shorten systole as a whole (I + E). The reduced force and duration of contraction are related to the shorter period of filling in the antecedent beat and, consequently, a reduction in presystolic size and initial length. Attention may be directed to the fact that the premature contraction starts at a higher initial tension, because it begins before relaxation of the previous beat has been completed. This is another illustration of a condition in which initial tension and length change in opposite directions and, as previously explained, the reactions seem to follow changes in initial length, not those in initial tension. However, the shorter initial length is not the dominant factor which determines the impairment of ventricular contraction.

The basic factor concerned was discovered in 1922[7] by comparing beats of the same cycle length excited from supraventricular and ventricular foci. Such records are shown in figure 15. The idioventricular beats (right) arise from the same initial tension as normal beats, thereby excluding secondary reactions to initial length. Nevertheless, beats due to direct ventricular stimulation display a longer isometric contraction (A–C), a prolongation of systolic ejection (C–F), and a conspicuously lower systolic summit. These changes are due to the abnormal order and spread of ventricular excitation from an idioventricular pacemaker. The concept developed is illustrated by the aid of the diagrams beneath the pressure curves of figure 15. During normal excitation (I) impulses are conducted with great speed to all fractions of the myocardium; hence a rapid summation of fraction-

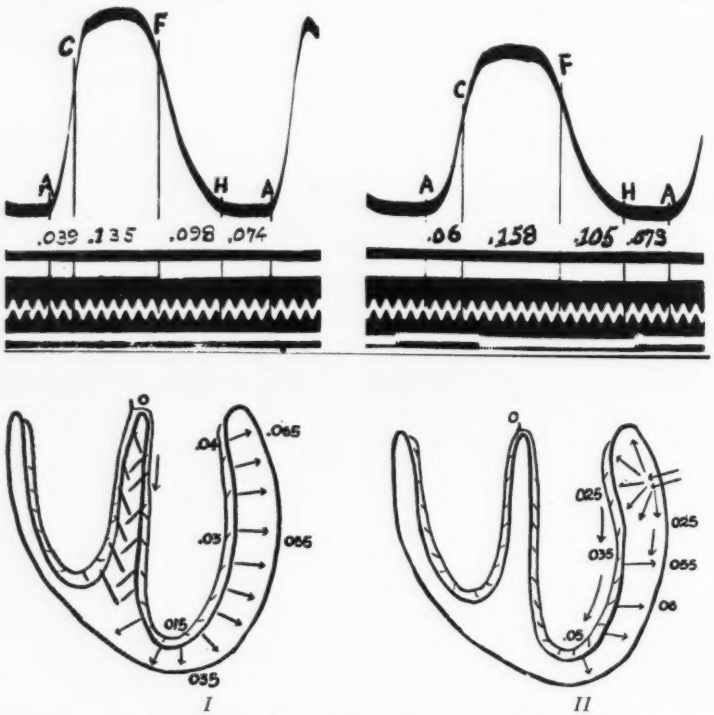

FIG. 15. Comparison of left ventricular pressure curves of same cycle length when excited over normal pathways (*I*) and from a ventricular focus (*II*). The diagrams below compare the approximate order, time, and direction of the excitation process during excitation from a supraventricular (*I*) and ventricular focus (*II*). Lettering as before. Note prolongation of isometric contraction (A-C) and ejection (C-F) in *II*. Time, .02 second. Discussion in text.

ate contractions takes place. When impulses arise from a ventricular focus (II), they spread more slowly at first and in a random fashion with the result that the phasic entry of contractions is delayed. As analyzed elsewhere,[6] this results in prolongation of contraction and development of less maximal tension. In addition, the order and direction of spread of the ventricular excitation process determines the mechanical efficiency of contraction. During normal excitation over bundle branches, the interventricular septum is primarily excited and contracts first. A rigid fixation is thus provided around which the ventricular muscle scrolls can contract and empty the ventricles efficiently. When excitation arises from the ventricular focus, impulses eventually reach the bundle branches, but they travel in a reverse direction; the septum is excited last and from apex to base. The resulting contraction of the ventricle as a whole would appear to be less efficient and may contribute to the lower pressure developed during systolic ejection.

To summarize, idioventricular beats are less efficient than normal ones because the ventricular pattern of contraction is affected by two factors: (a) the abnormal sequence in which fractionate contractions develop, and (b) the changes in ventricular filling which occur when the diastole of a preceding beat is abridged. The former retards the rate of pressure development and prolongs contraction, but reduces the maximal pressure developed. The latter contributes to the slow development of tension and lower systolic pressure through changes in initial length, but reduces the period of contraction to such an extent that the lengthening effect due to aberrant excitation is overbalanced, hence the ejection phase shortens.

Ventricular Alternation

It appears to be the consensus that ventricular alternation is a primary disorder involving abnormal excitation and/or contraction of myocardial fractions. In 1914, Wenckebach[29] advanced cogent a priori reasons for the concept that some types of alternation may be induced and sustained by hemodynamic mechanisms which cause alterations of ventricular filling in alternate beats. The question therefore arose whether there are two types of ventricular alternation, myogenic and dynamic, and, if so, whether means exist for their differentiation.

One of the first questions that interested me[30] in the study of alternation was whether the large as well as the small beat of an alternans couple is abnormal. When records were fortuitously obtained at the moment when alternation started spontaneously the surprising discovery was made that the larger beat of an alternans couple is never smaller than the preceding normal one, and frequently is even larger (fig. 16, curves I, II). In such supernormal

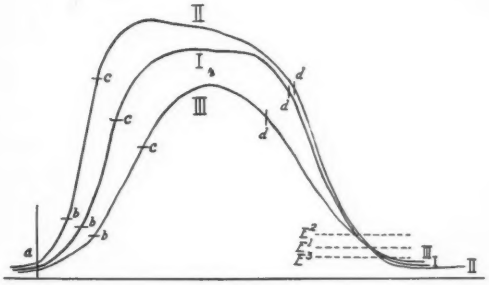

FIG. 16. Transcribed curves of left ventricular pressure: I, control curve before alternation, II, larger beat, and III, smaller beat of an alternating couple. Lettering as before. E_1, E_2, and E_3 indicate the effect that different levels of atrial pressure may have on the time when ventricular inflow begins.

beats the gradient of isometric contraction is a trifle steeper, and systolic ejection and total systole are both a trifle longer than in preceding normal beats. It would appear that the large alternans beat involves no fewer contracting fractions than a preceding normal one. Several explanations for such supernormal beats are possible: (1) A state of potential alternation may exist in the beats regarded as normal, that is to say, an equal number of contracting fractions may be deleted in every beat. (2) The increased amplitude and duration may be secondary to a slight increase in presystolic size and initial tension which for some reason accompanies the onset of alternation (fig. 16, curve II).

The dynamic differences between large and small beats of an alternans couple are illustrated by curves II and III of figure 16. The smaller

beat starts from a slightly lower presystolic pressure, it displays a more gradual isometric gradient, a longer isometric phase (a–c), a shorter systolic ejection phase (c–d), and a shorter period of total systole (a–d). These changes were attributed by Kahn[31] to deletion of contracting fractions. Since pressure also degrades more slowly during isometric relaxation (d–e), Straub[32] laid greater stress on differences in relaxation, concluding that "alternans developed only when the heart rate is so fast or the contour of the pressure curves so broad that the pressure does not have sufficient time to decline before the next ventricular excitation supervenes."

FIG. 17. Aortic (upper) and left ventricular (lower) pressure curves showing the development of temporary alternation (1, 2, 3, 4) after a compensatory pause (C), following a premature contraction (P). N is a normal beat. Time, .04 second.

During an investigation of premature ventricular systoles, the observation was made that a temporary alternation often follows a long diastolic pause.[33, 31] A typical response is shown in figure 17. A premature systole (P) succeeds a normal contraction (N). The long compensatory pause (C) allows greater filling of the ventricles and elevates initial tension slightly. This could account for the larger and prolonged post-compensatory beat.[1] However, it is not at once obvious why beat 2 is so much smaller and why alternation persisted in beats 3 and 4, and in two more beats not included in the record. Further studies revealed that similar reactions follow brief vagal stimulation or a temporary A-V block. Volume curves of the ventricles, such as are reproduced in figure 18, demonstrate that the rate of diastolic inflow is slower in the smaller beat, but since the ventricular expulsion is less complete, the presystolic volume and initial length preceding the larger beat are greater.[32] On the basis of such results I concluded that alternation can arise during the period of readjustment from a momentary increase in diastolic size. It was emphasized, however, that such alternation is temporary and takes place only when the heart beats rapidly. It is therefore probable that a tendency to alternation exists previous to the disturbance of ventricular filling.

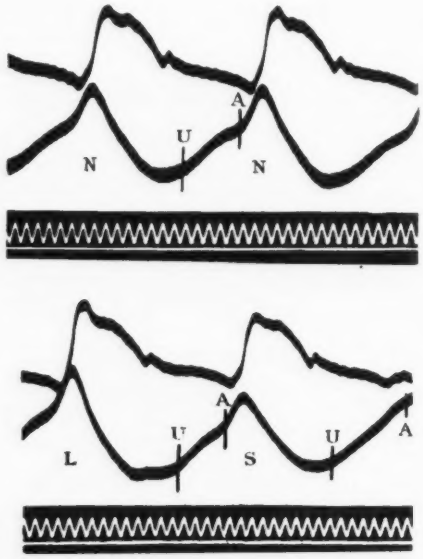

FIG. 18. Two sets of aortic pressure pulses and ventricular volume curves; systolic emptying indicated by downstroke in the latter. Upper set, normal beats; lower set, changes in larger beat (L), and smaller beat (S) after development of alternation. The stroke volume of smaller beat (S) is less complete and is followed by more gradual filling (U-A). The stroke volume of the larger beat exceeds that of normal ones shown in the upper set. Discussion in text. Time, 0.02 second. (After Wiggers,[1] fig. 47)

Summarizing my current views, it appears highly probable that ventricular alternation always involves the defection of some fractionate contractions during the smaller beat. However, changes in the intensity of alternation do not necessarily signify quantal variations in the deletion of fractionate contractions. They can be induced by secondary dynamic factors which alter diastolic distention and initial tension. For example, if the residual volume of blood is suddenly increased during a smaller contraction, the addition of a normal inflow volume during succeeding relaxation leads to a larger presystolic volume and initial tension, with the result that the amplitude of the larger contraction is augmented. It is for such dynamic reasons that a casual irregularity may intensify an existing alternation.

While ventricular alternation usually involves deletion of fractions distributed throughout the myocardium, it may be caused by alternate changes of contraction in only one region. The fact that periodic interruption of blood flow in a coronary ramus frequently results in alternation of the ventricle as a whole afforded Green[35] an opportunity to study the dynamics of alternation accompanying coronary insufficiency. Myographic records from the region of impaired blood supply revealed that three types of alternation may occur: (1) The region may shorten less during the smaller than during the larger beat. (2) It may shorten during the larger and actually stretch during the smaller beat, indicating alternate absence of contractions. (3) It may expand in both the small and the large beats, but to a lesser extent in the latter. Green[35] also found that the surface fibers in an ischemic area are stretched to a greater extent before inception of the smaller beats than previous to the onset of the larger ones. He interpreted this as proving that alternation following coronary insufficiency is due to periodic deletion of contractile units and not to alternate responses to changes in initial length. Further support for the localized source of alternating beats in myocardial ischemia was recently offered by the observations of Hellerstein and Liebow.[36] They reported that the S-T segment and T wave, more rarely the QRS complex, alter in epicardial leads from regions overlying the involved area.

These discussions of alternation following coronary insufficiency offer a natural transition to our next topic.

Coronary Occlusion—Myocardial Ischemia

The immediate dynamic effects following experimental coronary occlusion were first analyzed by Orias[37] and have recently been confirmed by Kupfer.[38] Representative immediate effects are shown in segment *B*, figure 19*A* and *B*. Within a minute after interruption of coronary flow, aortic pressures and pulse pressure are reduced, and the form of the aortic pressure pulse is altered; two phenomena that definitely indicate immediate reduction in systolic discharge. The left ventricular pressure curves furnish the explanation for such ventricular impairment. The isometric pressure rise is slower, but, since the semilunar valves open at a lower pressure, this phase may not be prolonged. The period of systolic ejection is abbreviated considerably, and the pressure summit is lower and more rounded. Orias,[37] applying basic information gained from my previous studies,[6] inferred that these immediate changes are caused by a deletion or impairment of contractions in the block of myocardium within the territory of the occluded vessel. In 1935, Tennant and I[8] demonstrated objectively by myographic tracings that this interpretation is correct. As shown in figure 20*II*, approximately within a minute after coronary occlusion, the ischemic area no longer shortens but expands brusquely during isometric contraction and either remains so during the remainder of systole or undergoes a slight shortening. Given such a hint through experimental observations, a number of investigators[39–43] have subsequently shown by means of fluoroscopic, roentgenographic, and electrokymographic technics that the infarcted area in human cases expands in a similar fashion. Such defective contraction in the potentially infarcted area reduces the total myocardial force for raising intraventricular pressure. In addition, some of the pressure created by still viable portions of the myocardium is spent in stretch-

ing the ischemic area, and is thus unavailable for expelling blood into the aorta.

As shown in segment *C* of figure 19, taken four minutes later, the heart has compensatory mechanisms by means of which dynamic conditions can be quickly restored to normal, provided the remaining myocardium is in good condition. While this interpretation accords with the general clinical opinion, the experiments just quoted are, to my knowledge, the only ones on record which really demonstrated that compensation occurs, not through improvement of collateral circulation in the affected area,[44] but through enhanced action of the uninvolved myocardium. Experiments such as these also elucidate the mechanisms by which the rest of the muscle responds promptly and compensates through increase in diastolic size and elevation of initial tension.[45] Briefly, the following chain of events takes place: During hypodynamic beats, such as are exhibited in segment *B*, the ventricles expel less blood; the accumulating systolic remainders added to oncoming blood progressively increase the presystolic volume and pressure in the left ventricle and stretch the viable muscle; this muscle, in accordance with the law of initial tension and length, contracts more vigorously, thereby restoring cardiac output and arterial pressures to normal. Such compensation is illustrated in segment *C*.

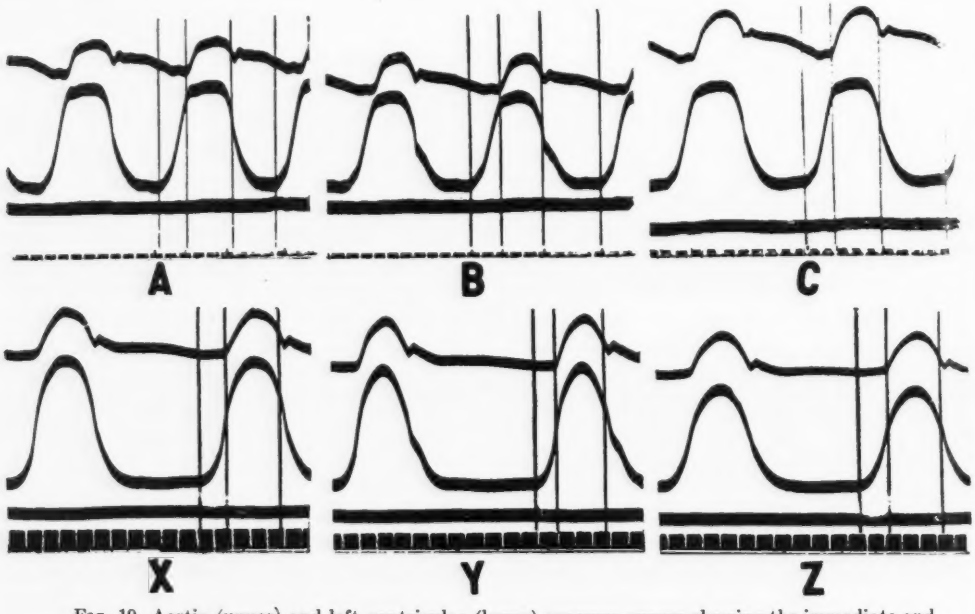

FIG. 19. Aortic (upper) and left ventricular (lower) pressure curves showing the immediate and delayed effects following occlusion of the ramus descendens anterior. *A*, control; *B*, one minute after coronary occlusion; *C*, compensation four minutes after occlusion. *X*, control from another experiment: *Y*, effect two minutes after coronary occlusion; *Z*, decompensation 15 minutes after occlusion. Discussion in text.

If, on the contrary, the viable ventricular muscle is not in good responsive condition, progressive deterioration supervenes. Segments *X*, *Y*, and *Z* of figure 19, taken from another experiment, illustrate this type of response. The ventricular pressure summit lowers steadily, systole is shortened, and arterial pulse pressures fall progressively despite the fact that initial tension rises steadily. As far as my experimental evidence goes, the circulatory failure which follows is entirely due to myocardial decompensation; there has never been evidence in our studies which indicates that peripheral factors

are involved in the circulatory failure.[38, 44, 45] Circulatory imbalance may also supervene through the development of cardiac irregularities. For instance, repeated premature contractions or atrial fibrillation displace blood from the arterial to the venous side and to the pulmonary vessels, with the result that a significant hypotension may develop and is often confused with a true state of shock.

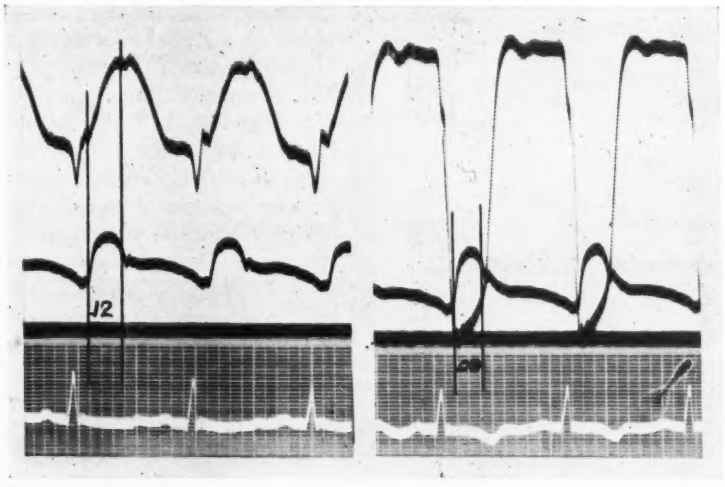

FIG. 20. Two records of myograms from the anterior surface of the left ventricle (upper curve) with aortic pressure pulses and an electrocardiogram (lead II). *I*, a normal control. *II*, records obtained two minutes after occluding the ramus descendens anterior. Note that in *I* shortening of the area is indicated by an upward deviation of the curve, while in *II* marked expansion is demonstrated by a downward movement between the two vertical lines.

THE IMPORTANCE OF CARDIAC VALVES

Yandell Henderson[46] pointed out that the A-V and semilunar valves cause the ventricles to contract and relax in a manner similar to that of a skeletal muscle attached to an instrument devised by Fick and known as a work adder. As illustrated in figure 21, the upper end of a muscle is attached to a stiff spring which can be arranged to record the muscular tension before and during contraction. The lower end of the muscle is attached to a movable lever on which a small weight is hung. This weight, which corresponds to the input load of the ventricles, lengthens the muscle slightly and creates a small tension previous to contraction (initial length and tension). A ratchet AV upon the toothed wheel of the work adder, comparable to the A-V valves, prevents the lever from moving until sufficient tension has been developed to overcome the force of a larger weight attached to the toothed wheel. This weight, which corresponds to the output load of the ventricle, is supported during the phases of isometric contraction and relaxation by a second ratchet SL, which corresponds to the semilunar valves. Such an arrangement causes the muscle to contract in an *afterloaded* manner.

If we release the ratchet SL, the large load acts upon the muscle before contraction starts and a *loaded* type of contraction results. A similar situation might be expected when the aortic valves are grossly incompetent. If we release the ratchet AV, no connection exists with the large wheel to which the heavier weight is attached; hence contraction of the muscle would merely raise and lower the small weight and never move the large one. A similar situation might be postulated during gross mitral incompetency, namely, that blood would merely be moved back and forth between the left atrium

and ventricle without any discharge into the aorta. Obviously, neither of these postulated effects actually takes place in the heart, which can still propel blood after deletion of all valves. The physical and physiologic reactions which make this possible need to be considered.

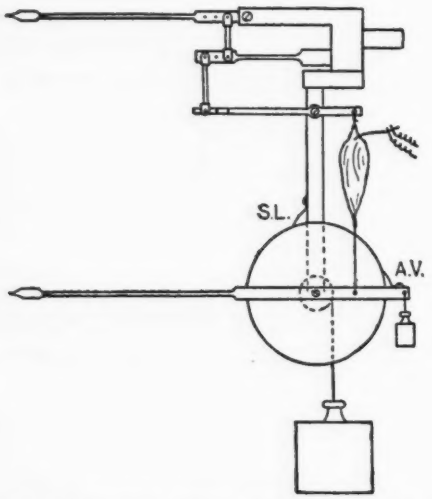

FIG. 21. Diagram illustrating the principle of Fick's work adder. Description in text. (After Y. Henderson[46])

AORTIC REGURGITATION

The dynamics of this valvular lesion which has interested me since 1915 involves three problems: (1) the mechanisms by which systolic discharge is essentially restored to normal, (2) the time of regurgitation during diastole, and (3) the factors which determine the regurgitated volume. (For bibliography see references 25, 47, 48.)

The immediate effect of an aortic leak is a reduction in the net stroke volume, a smaller aortic pulse pressure, and an increase in the diastolic ventricular volume. When the myocardium is in good condition it responds at once to the greater initial length and tension with a more vigorous contraction. As a result the tidal volume expelled from the ventricle increases considerably. The loss of pressure which occurs during diastole results in a very low end diastolic pressure in the aorta. Since systolic pressure is generally elevated through the augmented systolic discharge, the aortic pulse pressure is extremely large. These changes are illustrated in figures 22 and 23.

Miss Maltby and I[49] discovered that the reaction patterns of the left ventricle depend to a considerable extent on the size of the aperture. The effects produced by small leaks are shown in figure 22. The initial tension is increased at A and the isometric contraction phase (A–C) is shorter because expulsion of blood starts at a lower aortic pressure (C). The increased durations of ejection (C–F) and of total systole (A–F) are reactions to the higher initial tension. The summit of the pressure curve is reached earlier, because the ventricle empties itself more completely during the early portion of ejection when aortic pressure is still subnormal. Summarizing, the pattern of ventricular contraction as exhibited by the form of left ventricular pressure curves is a resultant of (1) the lowered aortic resistance during the early part of contraction, and (2) the compensatory effect produced by a greater presystolic stretch and elevation of initial tension.

When the aortic leaflets are spread wide apart so as to allow maximum reflux during diastole, the pattern of ventricular contraction is further changed because the full aortic load plays on the left ventricle and it contracts in a loaded manner. Such contractions tend to be of shorter duration than isometric types of contraction. The effects on left ventricular pressure curves are illustrated in figure 23. The elevation of initial tension is unquestionably responsible for the development of a higher systolic pressure and the ejection of larger tidal volumes into the aorta. The latter can be inferred directly from the large aortic pulse pressure which starts from a lower diastolic pressure. However, in the majority of cases, the expected lengthening of total systole is neutralized by the altered mode of contraction previously discussed.

It might be expected that an isometric contraction period could not exist in a loaded contraction. Actually, records that are reproduced in figure 23 indicate that a brief rise of ventricular pressure (A–C) still occurs before aortic pressure starts to rise. This delay is explained by the facts that the current of blood

in the ventricle must be reversed and that aortic diastolic pressure slightly exceeds that in the ventricles.

The records of figures 22 and 23 show clearly that the time of diastolic regurgitation depends on the size of the aortic orifice. With openings of small and moderate size (fig. 22) the gradient and duration of isometric relaxation remains unaltered, the chief decline of aortic pressure occurring after completion of isometric relaxation at I. Hence the inference that significant regurgitation does not take place until relaxation has progressed to a pressure level at which the mitral valves open. In this way a dynamic situation is created in which flow from the left atrium competes for ventricular space with that through a leaking aortic valve.

On the contrary, when the semilunar valves are widely separated, aortic pressure falls abruptly to a low level during the time the left ventricle relaxes (fig. 23, F–I), and aortic pressure declines comparatively little during the remainder of diastole. The inference follows logically that, in very large leaks, regurgitation takes place immediately during the decrease of ventricular tension. It may be added parenthetically that this period corresponds to isometric relaxation in the normal heart but cannot be designated as such since the ventricle contracts as a loaded, not as an afterloaded, muscle. The slow elevation of tension after I in figure 23 is attributable to ventricular filling from the left atrium.

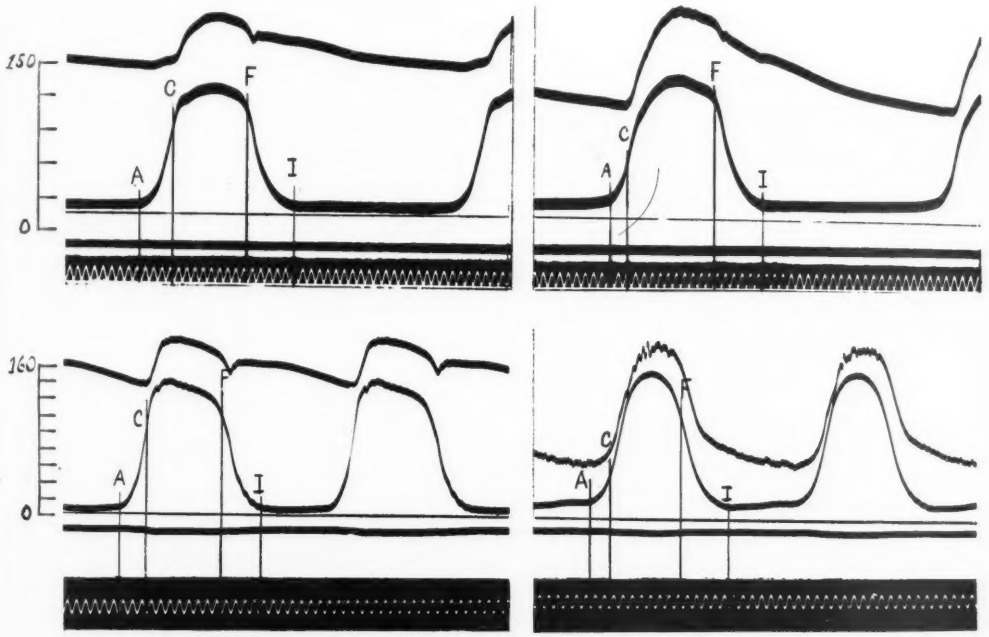

FIG. 22. (*Above*) Aortic and left ventricular pressure pulses demonstrating the characteristic changes produced by a comparatively small aortic leak. A-C, isometric contraction; C-F, ejection phases; F-I, relaxation to basic pressure levels. Time .02 second. Discussion in text.

FIG. 23. (*Below*) Aortic and left ventricular pressure pulses showing characteristic changes following a maximum aortic leak. Lettering as in figure 22. Discussion in text.

The influence that the size of the leaking aortic orifice has on the regurgitant volume has been studied from physical and engineering standpoints on models as well as on dead hearts. (For bibliography, see references 25, 47, 48). Experimental work has convinced us, however, that the magnitude of regurgitation depends as much on the successive pressure differences as on the size of the leaking orifice. As a matter

of fact, for purely physical reasons, the total pressure difference diminishes as the size of the leaking orifice increases. The hydraulic principles can be gleaned from the illustration in figure 24, in which aortic pressure curves simulating those obtained after large and small leaks are superimposed on a common ventricular pressure curve. The successive diastolic gradients in the case of larger leaks are represented by the area, C_X and those in the case of smaller leaks by the area $C_X + C_Y$.

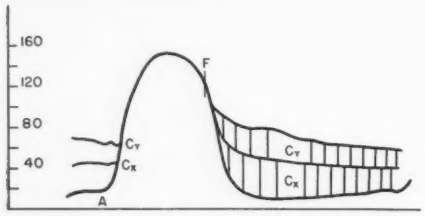

FIG. 24. Diagram showing that the diastolic pressure differential between aorta and left ventricle is less in the case of large sized aortic orifices (C_X) than in small ones ($C_X + C_Y$).

In former years I defended the view previously suggested by Stewart that the percentage of the tidal volume which regurgitates remains relatively small up to orifices which equal one-third that of the aortic ring. Subsequent observations of my own and of others reviewed elsewhere[48] indicate, however, that regurgitation volume may increase up to 60 per cent of the tidal volume with large aortic openings.

MITRAL INSUFFICIENCY

It is generally conceded on the basis of animal experiments that the reduction in systolic discharge which results from reflux of blood into the left atrium is somehow compensated by mobilization of a larger tidal volume. In 1922 Feil and I[50] elucidated the compensatory mechanisms concerned through registration of pressure pulses from the left atrium and ventricle. Our studies indicated that the sudden creation of a mitral leak is succeeded by the following train of events: By virtue of the systolic backflow through incompetent valves the volume of blood discharged into the aorta during each systole is reduced. As illustrated in figure 25, maximal ventricular tension is lowered immediately, but increases gradually as initial pressure rises. At the same time the pressure in the left atrium increases, and the curves show a marked systolic elevation with murmur vibrations superimposed. Under the greater head of pressure at F the left ventricle fills more completely, and the effects of augmented initial tension and presystolic volume come into play. Maximal intraventricular pressure increases steadily, and the duration of systole is slightly prolonged.

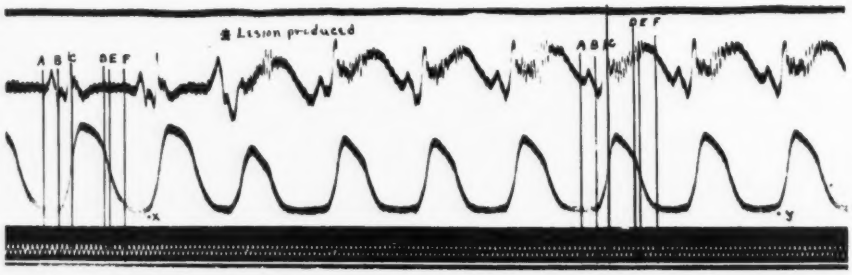

FIG. 25. Pressure curves in left atrium (upper) and left ventricle (lower) illustrating immediate and stabilized effect of rendering the mitral valves suddenly insufficient. A-B, atrial systole; B-C, isometric ventricular contraction; C-D, ejection phase; E-F, isometric relaxation. Time, .02 second. Note superposition of systolic murmur vibrations on atrial curve. Description in text. (After Wiggers and Feil[50])

The records of figure 25 show other interesting details. Comparisons of phasic pressure changes in the left atrium and ventricle demonstrate that even when a static equilibrium has been reached, left atrial pressure rises only

to a minimal extent during isometric contraction, indicating that no significant regurgitation takes place during this phase. The main elevation of left atrial pressure and the real regurgitation occur simultaneously with dis-

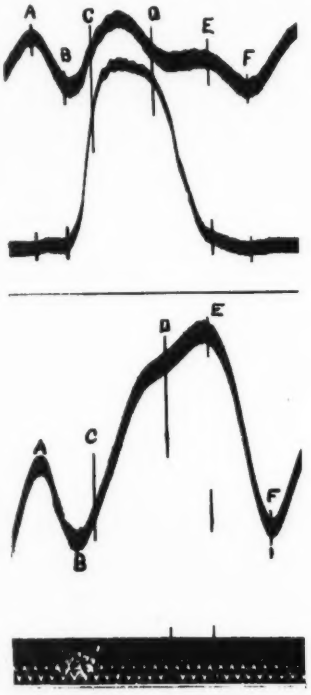

FIG. 26. Volume changes of the left atrium related to a left ventricular pressure curve. Upper volume curves during normal action of A-V valves. Lower volume curves adjusted to same ventricular pressure curve, but taken after production of mitral insufficiency. A-B, decrease in atrial volume during atrial systole; B-C, slight increase in volume during isometric contraction in both curves; C-D, more marked increase in volume during systolic ejection in lower curve; D-E, continued volume increase during isometric relaxation in lower curve; E-F, more marked reduction in atrial volume during rapid inflow phase in lower curve. (After Wiggers and Feil[50])

charge of blood into the aorta. Furthermore, regurgitation does not terminate precisely with systole, for atrial pressure continues to rise at a reduced rate during the period of isometric relaxation. These times of regurgitation are corroborated by registration of volume changes of the left atrium by special forms of cardiometers. Such records are shown in figure 26. When regurgitation exists, the left atrial volume decreases during atrial systole (A–B), increases very little during isometric ventricular contraction (B–C), augments rapidly and considerably during the period of systolic ejection (C–D), and continues to increase for 0.08 second during isometric relaxation of the ventricle (D–E). During the succeeding rapid inflow phase (E–F), the volume of the left atrium decreases rapidly as it empties into the left ventricle.

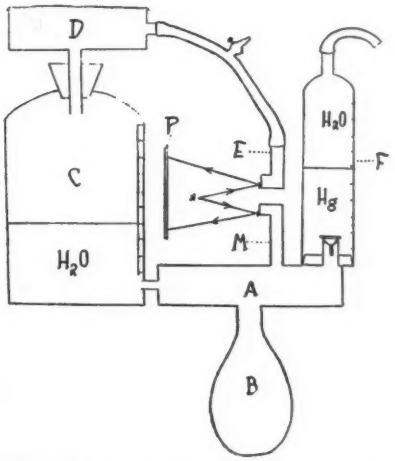

FIG. 27. Physical model to demonstrate regurgitation and forward movement of a liquid. Description in text. (After Wiggers and Feil[50])

Physical factors alone account for such a time course of regurgitation. Since the isometric contraction phase is very short (0.04 to 0.05 second) and the pressure increases roughly from 4 to 70 mm. Hg, the inertia of blood within the ventricle cannot be quickly overcome, and the blood is not set in backward motion until the aortic valves have opened. Thus any considerable reflux is dynamically impossible even when openings of considerable size exist. On the contrary, systolic ejection lasts from 0.15 to 0.25 second and the intraventricular pressure ranges from 70 to 160 mm. Hg. The continuance of such pressures over a longer time interval determines the consider-

able backflow during systolic ejection. Finally, since ventricular pressure still exceeds intra-atrial during isometric relaxation, equal to 0.8 to 0.09 second, regurgitation continues despite the fact that diastole is actually in progress.

That these types of regurgitation do not involve mechanisms peculiar to the heart, but are determined by physical factors, can be demonstrated successfully by simple apparatus illustrated in figure 27. The device consists of a chamber (A) to which an optical manometer (M) recording the pressure within it is attached.

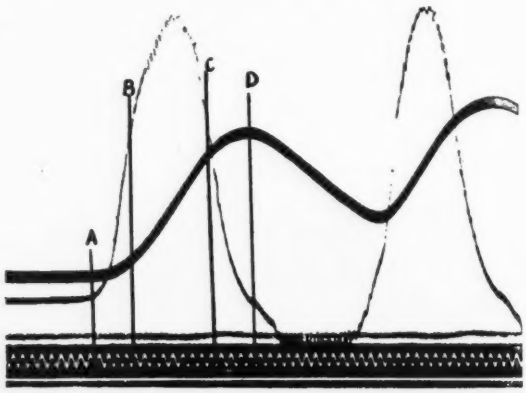

FIG. 28. Records of pressure (lighter curve) and periods of regurgitation obtained when bulb of apparatus shown in figure 27 is compressed to simulate ventricular pressure changes: A-B, isometric rise of pressure; B-C, period of output into mercury chamber; C-D, relaxation of bulb. Description in text. (After Wiggers and Feil[80])

The pressure is increased by rapid compression of a large bulb (B). Fluid is thus displaced either through a valveless tube into a bottle (C) against a fluid column varying from 60 to 150 mm. H_2O, or by a larger tube through a valve into a second receptacle (F) containing a mercury column equal to 60 or 80 mm. Hg. Time relations of regurgitation to pressure development, as well as the volume actually regurgitated into the bottle (O) under different pressure conditions may be optically recorded by connecting the bottle (C) to a tambour (D) attached to an optical capsule (E).

Figure 28 shows a record in which the pressure variations in the system simulate those in the heart. As pressure rises rapidly to a point corresponding approximately to the isometric phase (A–B), the regurgitation is exceedingly slight. During the subsequent rise and fall of pressure (B–C), corresponding roughly to the ejection phase, a larger volume is regurgitated. As in the heart, this backflow does not cease when compression is stopped at C, but continues until D. It can also be demonstrated that such a physical phenomenon is conditioned upon a rapid compression of the bulb. If the bulb is squeezed very slowly and the pressure elevated very gradually, backflow starts at once, and regurgitation becomes large during the isometric period, which is thereby also prolonged. The bulb may indeed be compressed so slowly that its entire contents are emptied into the bottle. The inference is clear; the volume of regurgitation is conditioned not only by the size of the leak and the mean pressure in the ventricle, but also by the velocity of tension development during isometric contraction. Given the same orifice, more blood regurgitates when ventricular contractions become hypodynamic.

Herein lies the real compensatory importance of good muscular action during mitral insufficiency. Failure of the myocardium to respond adequately to the increase in initial tension results in a series of events which end in decompensation. The seriousness of the valvular lesion consists in the fact that the patient or

animal with incompetent mitral valves has lost a factor of safety by which slight cardiac depression can be readily withstood. Mitral insufficiency is dangerous primarily, not by virtue of the circulatory changes induced through valvular deficiency, but on account of the constant liability to decompensation from any cause which weakens ventricular contraction. Finally, attention may be directed to the fact that since the rate of pressure increase is such an important determinant of the volume regurgitated, calculations of the size of leaking orifices from laws based on static equations do not necessarily apply to the beating heart.

Summary

I have endeavored to review selected types of experiments carried out in our laboratory during the past 33 years which I consider relevant to the interpretation of clinical disorders. From an analysis of ventricular pressure pulses inferences were drawn as to basic determinants of cardiac performance in experimental conditions simulating those which arise clinically. The analysis included alterations in ventricular contraction patterns produced by pericardial effusion, hypervolemia, oligemia, arterial hypertension of peripheral origin and that due to coarctation of the aorta, aortic and pulmonary stenosis, idioventricular rhythms, ventricular alternation, coronary occlusion and myocardial ischemia, aortic regurgitation, and mitral insufficiency.

1. The following principles were emphasized for guidance in interpreting ventricular pressure curves: Investigators who attempt to analyze the mechanisms of cardiac adaptation from ventricular pressure pulses should first satisfy themselves that the recorded curves accurately depict the pressure changes, i.e., that they are not deformed by artefacts or that, when present, these can be discounted. They must be able to translate changing pressure values, gradients, and inflections presented by ventricular pressure curves into mental pictures of dynamic processes. The integration of pressure pulses from the left atria, ventricle, and aorta with myographic and acoustic phenomena, volume changes in the ventricles, and electrical phenomena, once considered an academic exercise, has become an inescapable requirement in the current era of hemodynamic investigations.

2. As Starling has pointed out, the responses of the myocardium under many normal and pathologic conditions are determined by changes in the presystolic size of a ventricle, that is, the initial length of its fibers. Personal experience has confirmed Frank's earlier postulate that under ordinary conditions changes in initial length are produced by alterations in ventricular pressure at the onset of contractions, that is, the initial tension.

3. The law of initial length and tension so formulated assumes the existence of controlled conditions. Consequently, their determinant effect on force, magnitude, and duration of contraction can be satisfactorily studied only when the following conditions obtain: (a) the cycle length must remain constant, (b) the basic condition of the myocardium must remain the same, otherwise its response varies at identical initial tension and length, and (c) conditions which change the mode of ventricular contraction in mechanical ways must not be operative.

4. Under such controlled conditions, changes in the force, amplitude, and duration of ventricular pressure curves accompanied by an elevation of initial tension can be referred to the beneficial effects of stretch. Such a dominant control of the contraction patterns is illustrated by responses to increased and decreased venous return during respective states of hypervolemia and oligemia.

5. When the reactivity of the myocardium is enhanced or depressed through local metabolites, fatigue, humoral agents, nervous actions, or inadequate coronary flow, the ventricular responses alter without changes in initial tension or more commonly with changes in an opposite direction. Thus, following the use of cardiac depressant drugs or prolonged hypotension such as occurs in shock, the force, magnitude, and duration of ventricular contractions decrease through primary myocardial depression, and this leads to elevation of initial length and tension.

6. Under special conditions, initial tension and length may deviate in opposite directions, in which case the reactions are determined by changes in initial length. This happens during

large pericardial effusions, for the elevated pericardial pressure is transferred to the ventricular cavity at the same time that diastolic filling is hindered. The ventricles develop less pressure and their contraction is abridged despite an elevation of initial tension. A similar dissociation of initial tension and length supervenes when a premature ventricular systole starts before the preceding beat has relaxed completely. Mechanical impairment of filling also operates to dissociate initial tension and pressure in ventricular tachycardia and alternation, but it is not basically important in determining the contraction pattern.

7. The slower and smaller contractions displayed by beats of ventricular origin are produced by a slower entry of fractionate contractions combined with failure to fix the septum primarily. Similarly, the apparent depression of myocardial contraction exhibited by the smaller beat of an alternans couple is caused by deletion of some fractionate contractions. There is no evidence that the inherent reactivity of muscle fractions participating in contraction is changed. There is good evidence that they respond to secondary changes in initial tension and length which may either augment or counteract the effect of aberrant myocardial contractions. Depression of ventricular contraction which follows coronary occlusion almost immediately is likewise due to enfeeblement or absence of contraction in the infarcted area, but complete compensation may result from response of viable muscle to increases in initial tension and length. On the other hand, myocardial depression may supervene and intensify the hypodynamic response of the left ventricle, leading to circulatory failure.

8. It must be obvious from data so far analyzed that the establishment of concordant or discordant changes in initial tension (or atrial pressures) and contraction patterns in uncontrolled or abnormal conditions cannot be cited to validate or invalidate the operation of the law of initial tension and length.

9. A careful study of left ventricular pressure curves has revealed that the law of initial tension and length determines the ventricular responses under grossly abnormal conditions, but the resulting contraction patterns are modified more or less through operation of other coefficients. (a) In aortic hypertension due to increased peripheral resistance the force of contraction is enhanced and its duration tends to be curtailed through action of a greater output load. (b) In aortic coarctation the ventricular effects of increased resistance and rise of initial tension are decidedly modified by the fact that the left ventricular contents must be displaced into a smaller and less distensible compression chamber. (c) In aortic stenosis the effects of increased initial length and augmented resistance on ventricular contraction are modified by the shift from an afterloaded to a more nearly isometric type of contraction. (d) In severe aortic insufficiency the increased initial length and tension are responsible for the compensatory increase in force of contraction, but their effects on the ventricular contraction pattern are modified through a shift from an afterloaded to a loaded type of contraction. (e) Existence of incompetent mitral valves modifies the ventricular response through changes in initial tension, but the ventricular contraction pattern is modified because a part of the tidal volume regurgitates into the left atrium.

In conclusion, if an apology is needed for dwelling so largely on personal observations and on those of close personal associates, it is that deductions emerging from one's own experiments are apt to be more convincing than those formulated on the data of others, that in most instances the basic determinants of cardiac behavior established in diverse circulatory derangements have some claim to priority, that their validity has been tested in many unreported experiments, and that this is not the occasion to defend my results or postulates against those who have reason to question their correctness on the basis of their own studies. An investigator cannot hope to convince everyone of the correctness of his views; he will have acquitted himself honorably if he has sincerely convinced *himself* of the accuracy of his data and the reasonableness of the inferences drawn therefrom. This I have done to the best of my ability.

REFERENCES

[1] WIGGERS, C. J.: Pressure Pulses in the Cardiovascular System. New York and London, Longmans, Green, 1928.

[2] —: Physiology of Shock. New York, The Commonwealth Fund, 1950 (Cambridge, Mass., Harvard University Press).

[3] —: Studies on the consecutive phases of the cardiac cycle. I. The duration of the consecutive phases of the cardiac cycle and the criteria for their precise determination. Am. J. Physiol. **56:** 415, 1921.

[4] —: The electrocardiogram; its relation to cardiodynamic events. Arch. Int. Med. **20:** 93, 1917.

[5] —: The independence of electrical and mechanical reactions in the mammalian heart. Am. Heart J. **1:** 173, 1925.

[6] —: Interpretation of the intraventricular pressure curve on the basis of rapidly summated fractionate contractions. Am. J. Physiol. **80:** 12, 1927.

[7] —: The muscular reactions of the mammalian ventricles to artificial surface stimuli. Am. J. Physiol. **73:** 346, 1925.

[8] TENNANT, R., AND WIGGERS, C. J.: The effect of coronary occlusion on myocardial contraction. Am. J. Physiol. **112:** 351, 1935.

[9] WIGGERS, C. J.: Studies on the cardiodynamic actions of drugs. I. The applications of optical methods of pressure registration in the study of cardiac stimulants and depressants. J. Pharmacol. & Exper. Therap. **30:** 217, 1927.

[10] —: Determinants of cardiac performance. Circulation **4:** 485, 1951.

[11] PATTERSON, S. W., PIPER, H., AND STARLING, E. H.: The regulation of the heart beat. J. Physiol. **48:** 465, 1914.

[12] CANNON, W. B., AND CATTELL, McK.: Experimental traumatic shock; critical level in a falling blood pressure. Arch. Surg. **4:** 300, 1922.

[13] KUNO, YAS: Mechanical effect of fluid in the pericardium on the function of the heart. J. Physiol. **51:** 221, 1917.

[14] WILSON, J. A., AND MEEK, W. J.: Effect of the pericardium on cardiac distention as determined by the x-ray. Am. J. Physiol. **82:** 34, 1927.

[15] FINEBERG, M. H.: Functional capacity of the normal pericardium. Am. Heart J. **11:** 748, 1936.

[16] WIGGERS, C. J.: The dominant control of mammalian ventricular dynamics by initial length. Rev. Soc. argent. de Biol. Suppl. **10:** 546, 1934.

[17] —, AND KATZ, L. N.: The contour of the ventricular volume curves under different conditions. Am. J. Physiol. **58:** 439, 1922.

[18] GREGG, D. E., AND WIGGERS, C. J.: The circulatory effects of acute experimental hypervolemia. Am. J. Physiol. **104:** 423, 1933.

[19] OPDYKE, D. F., AND WIGGERS, C. J.: Studies of right and left ventricular activity during hemorrhagic hypotension and shock. Am. J. Physiol. **147:** 270, 1946.

[20] WIGGERS, C. J.: Studies on the consecutive cases of the cardiac cycle. II. The laws governing the relative durations of ventricular systole and diastole. Am. J. Physiol. **56:** 439, 1921.

[21] KATZ, L. N., AND WIGGERS, C. J.: The influence of high systemic blood pressures on the right ventricle and pulmonary circuit. Am. J. Physiol. **82:** 91, 1927.

[22] GUPTA, T. C., AND WIGGERS, C. J.: Basic hemodynamic changes produced by aortic coarctation of different degrees. Circulation **3:** 17, 1951.

[23] WIGGERS, C. J.: The influence of vascular factors on mean pressure, pulse pressure, and phasic peripheral flow. Am. J. Physiol. **123:** 644, 1938.

[24] —: Physiology in Health and Disease, ed. 5. Philadelphia, Lea & Febiger, 1949.

[25] WIGGERS, C. J.: Die pathologische Physiologie des Kreislaufs bei Klappenerkrankungen des Herzens. Ergebn. d. Physiol. **29:** 250, 1929.

[26] DE HEER, J. L.: Die Dynamik des Säugetierherzens im Kreislauf in der Norm. bei Aortenstenose und nach Strophanthin. Arch. f. d. ges. Physiol. **148:** 1, 1912.

[27] KATZ, L. N., RALLI, E. P., AND CHEER, S-N.: The cardiodynamic changes in the aorta and left ventricle due to stenosis of the aorta. J. Clin. Investigation **5:** 91, 1928.

[28] FINEBERG, M. H., AND WIGGERS, C. J.: Compensation and failure of the right ventricle. Am. Heart J. **11:** 255, 1936.

[29] WENCKEBACH, K. F.: Die Unregelmässige Herztätigkeit und ihre klinische Bedeutung. Berlin, Engelmann, 1914.

[30] WIGGERS, C. J.: The dynamics of ventricular alternation. Ann. Clin. Med. **5:** 1022, 1927.

[31] KAHN, R. H.: Zum Problem des Herzalternans. Arch. f.d. ges. Physiol. **181:** 65, 1920.

[32] STRAUB, H.: Dynamik der Herzalternans. Deutsch. Arch. f. klin. Med. **123:** 403, 1917.

[33] WIGGERS, C. J.: The cause of temporary ventricular alternation following a long diastolic pause. Proc. Soc. Exper. Biol. & Med. **24:** 386, 1927.

[34] —: The cause of temporary ventricular alternation following a long diastolic pause. Contributions to Medical Science, dedicated to A. S. Warthin. Ann Arbor, George Wahr, 1927. P. 65.

[35] GREEN, H. D.: The nature of ventricular alternation resulting from reduced coronary blood flow. Am. J. Physiol. **114:** 407, 1936.

[36] HELLERSTEIN, H. K., AND LIEBOW I. M.: Electrical alternation in experimental coronary artery occlusion. Am. J. Physiol. **160:** 366, 1950.

[37] ORIAS, OSCAR: The dynamic changes in the ventricles following ligation of the ramus descendens anterior. Am. J. Physiol. **100:** 629, 1932.

[38] KUPFER, S.: Can experimental shock be induced

by coronary occlusion? Proc. Soc. Exper. Biol. & Med. **76:** 134, 1951.

[39] GUBNER, R., AND CRAWFORD, J. H.: Roentgenkymographic studies of myocardial infarction. Am. Heart J. **18:** 8, 1939.

[40] SUSSMAN, M. L., DACK, S., AND MASTER, A. M.: The roentgenkymogram in myocardial infarction. I. The abnormalities in left ventricular contraction. Am. Heart J. **19:** 453, 1940.

[41] MASTER, A. M., GUBNER, R., DACK, S., AND JAFFE, H. L.: The diagnosis of coronary occlusion and myocardial infarction by fluoroscopic examination. Am. Heart J. **20:** 475, 1940.

[42] DACK, S., PALEY, D. H., AND SUSSMAN, M. L.: A comparison of electrokymography and roentgenkymography in the study of myocardial infarction. Circulation **1:** 551, 1950.

[43] SCHWEDEL, J. B., SAMET, P., AND MEDNICK, H.: Electrokymographic studies of abnormal left ventricular pulsations. Am. Heart J. **40:** 410, 1950.

[44] WIGGERS, C. J.: The problem of functional coronary collaterals. Exper. Med. & Surg. **8:** 402, 1950.

[45] —: The functional consequences of coronary occlusion. Ann. Int. Med. **23:** 158, 1945.

[46] HENDERSON, Y.: The volume curve of the ventricles of the mammalian heart, and the significance of this curve in respect to the mechanics of the heart beat and the filling of the ventricles. Am. J. Physiol. **16:** 325, 1906.

[47] WIGGERS, C. J.: Circulation in Health and Disease, ed. 2. Philadelphia, Lea & Febiger, 1923.

[48] —: The magnitude of regurgitation with aortic leaks of different sizes. J. A. M. A. **97:** 1359, 1931.

[49] —, AND MALTBY, A. B.: Further observations on experimental aortic insufficiency. Am. J. Physiol. **97:** 689, 1931.

[50] —, AND FEIL, H.: Cardiodynamics of mitral insufficiency. Heart **9:** 149, 1922.

The Responsibility of the Physician in the Selection of Patients with Mitral Stenosis for Surgical Treatment

By Dwight E. Harken, M.D., Laurence B. Ellis, M.D., Lewis Dexter, M.D., Robert E. Farrand, M.D., and James F. Dickson, III, M.D.

The anatomy of the mitral leaflets, a classification of the variations in pathologic morphology of rheumatic stenosis, and the evolution of a practical technic for relief of that stenosis while restoring valve action are considered. The life cycle of patients suffering from mitral stenosis is reviewed and a clinical classification of these patients is presented. Some indications and contraindications for surgery are discussed in the light of strength and weakness of present surgical methods. Results of surgical treatment are reviewed.

MANY people badly disabled by mitral stenosis are now being greatly improved by surgical treatment. To those of us who have lived through the troubled era when most of the patients died from attempts at surgical correction, it is gratifying to see properly selected patients subjected to operation with a mortality rate that is not high in relation to the severity of their disease. These results breed enthusiasm in surgeons that may be dangerous. Conversely, the lack of appreciation by physicians of the remarkable advantages that may accrue from the surgical treatment of mitral stenosis is equally dangerous. The possibility of a proper place for surgical intervention in the life cycle of the disease must be investigated carefully and objectively. If in certain phases of the life cycle of the disease surgical treatment is the best treatment, it becomes the responsibility of all participating in the care of the patient to see that the best treatment is given. It is the physician who first sees the patient and therefore it is he who must first bear this major responsibility. Theoretically, in order to assume this responsibility, he should know everything about the life cycle of mitral stenosis and rheumatic carditis; he should also know what medical adjuncts are to be developed in the near future; he should be cognizant of present surgical possibilities and of the surgery that can be expected in the near future. This is, of course, impossible. We can, however, do our best to approximate such a position on the basis of information now available. That is the purpose of this discussion.

The following will be discussed: first, a review of the anatomy of the normal mitral valve; second, the morphologic types of mitral stenosis; third, various indirect and direct forms of surgical treatment and their shortcomings; fourth, the life cycle of mitral stenosis; fifth, a clinical classification of patients in various phases of the life cycle; sixth, which patients should have surgical treatment *now* and which patients should be deferred in view of present surgical shortcomings.

The Leaflet Pattern in the Normal Mitral Valve

As a background for the study of mitral stenosis and regurgitation it has been necessary to examine the anatomy of the normal mitral valve. Knowledge of the normal assists in making surgical valvuloplasty more nearly

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restore the normal state. This has involved detailed gross examination of the mitral ring, its leaflets, chordae tendineae and papillary muscles in 35 consecutive normal hearts. The gross anatomic examination of the normal heart at autopsy was correlated with studies of the living animal heart and with clinical findings in diseased human hearts.

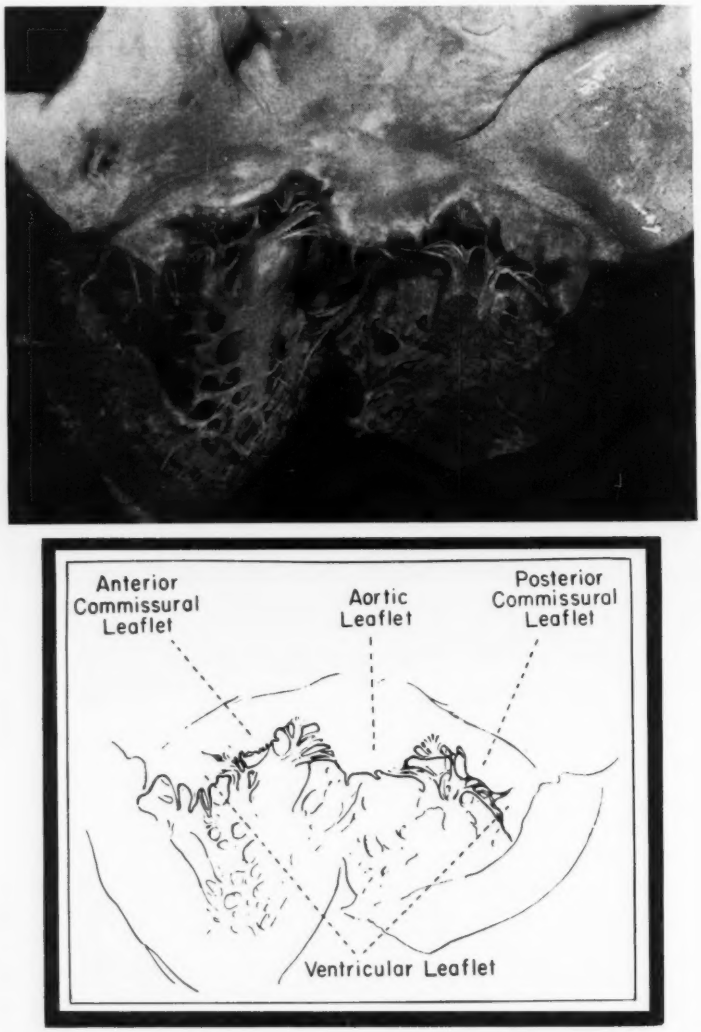

FIG. 1. This group, "normal," has four leaflets, triangular in shape, with their blunted apexes directed toward the center of the mitral orifice. The radial width of the aortic leaflet is approximately twice that of the ventricular leaflet. The two commissural leaflets may vary considerably in size but their width is usually two thirds that of the ventricular leaflet. This is the arrangement seen in 75 per cent of valves.

The findings revealed that there is considerable variation in the leaflet arrangement. In general, the valve structure consists of a continuous veil inserting around the entire

circumference of the mitral orifice. This continuous veil is divided into leaflets by clefts, none of which reach the attachment. This is at variance with the usual concept of two separate leaves. The most prominent triangular projections of the veil are the aortic and ventricular leaflets, with blunted apexes extending toward the center of the mitral orifice. However, two additional triangular projections are commonly found that might be called the "anterior and posterior commissural leaflets" (fig. 1). Four triangular leaflets, arranged circumferentially, constitute the mitral valve.

While the shape of all four leaflets is essentially similar, their size and distribution of chordae tendineae vary greatly. The aortic leaflet is the largest; its radial length from the mitral ring is approximately twice that of the ventricular leaflet. The two smaller commissural leaflets which arise from the lateral margins of the major (aortic and ventricular) leaflets are but one-half to two-thirds of the length of the ventricular leaflets. Though small and fragile in appearance, their function in maintaining the integrity of the redundant portions of the two larger valve leaflets in systolic closure seems to be considerable. A valve pattern, as seen in 75 per cent of these hearts, will be called the "normal" (fig. 1). In the remaining 25 per cent, variation is principally in the size and shape of the ventricular leaflet in relation to the two commissural leaflets. Instead of being triangular in shape, the ventricular leaflet may be oblong, bifid, trifid or even indistinguishably in continuity with one of the commissural leaflets. On occasion, the radial length of the aortic leaflet may be markedly foreshortened so that the ventricular leaflet may even be the larger. This is of little functional significance in the normal heart due to the redundancy of the aortic and ventricular leaflets. However, when the redundant portions are destroyed, fibrosed or calcified from rheumatic valvulitis, these variations may assume great importance. This could well be a substantial factor in the production of mitral insufficiency, when a fish-mouth stenosis in such a valve is closer to and facing into the outflow tract to the aorta.

Morphologic Classification of Mitral Stenosis

As previously described,[1] there are two basic morphologic patterns of mitral stenosis: Type I is primarily a rigid, fibrous contraction of the leaflets to a stenotic opening with little thickening or fusion of the chordae tendineae. If present, it is likely to occur around the rigid orifice and to extend anteriorly and posteriorly.

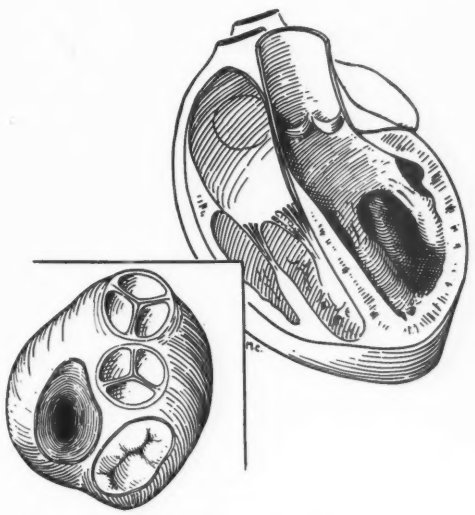

Fig. 2. *Type I mitral stenosis:* A common pattern of mitral stenosis with (a) marginal leaflet fusion and calcification, (b) leaflet flexibility remaining, (c) only minor thickening in fusion of the chordae tendineae, and (d) right ventricular and pulmonary artery enlargement.

More than 85 per cent of patients are dominantly of this type (fig. 2). Type II consists of an elastic funnel with marked fusion of the chordae tendineae. These fused chordae tendineae may even constitute secondary stenosis (fig. 3). Calcification is common in type I, rare in type II. Less than 15 per cent of patients with marked stenosis have dominant type II processes. There is a whole spectrum of variations of individual patterns of mitral stenosis from I to II. Furthermore, either of these types can have a valve orifice of given

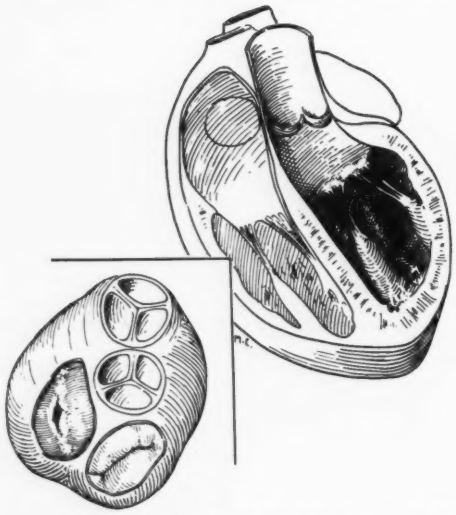

FIG. 3. *Type II mitral stenosis:* A less common but not unusual form of mitral stenosis with (a) a flexible funnel fusion of the leaflets, (b) fusion of the chordae tendineae, (c) no calcification, and (d) enlargement of the right ventricle and pulmonary artery.

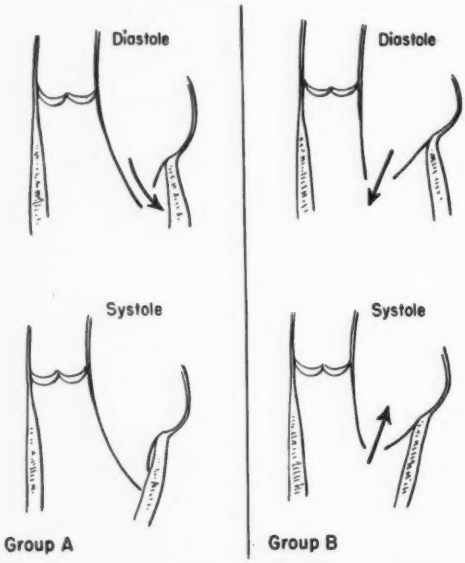

FIG. 4. *Group A:* The fish-mouth opening of the stenotic mitral valve funnel is directed *laterally* so that it is closed by the myocardium in systole. There is no regurgitation.

Group B: The fish-mouth opening of the stenotic mitral valve funnel is directed *medially* into the outflow tract and is not closed in systole. There is marked regurgitation.

size and yet may or may not be associated with regurgitation. If the mouth of the funnel is turned toward the myocardium, the ventricular wall may close the orifice in systole and prevent regurgitation. This is called group A (fig. 4). If the stenotic orifice rigidly held open by the pathologic process faces out into the cardiac outflow tract, there may be extensive regurgitation. This is called group B (fig. 4). Again, A represents one end of a spectrum of variations and B the opposite pole; any individual lesion may fall between. The use of such a classification facilitates descriptions and also focuses attention on a type of process that responds well to valvuloplasty (type I) and less well (type II).

INDIRECT SURGICAL METHODS FOR TREATING MITRAL STENOSIS

Formerly the difficulties attending direct intracardiac surgery prompted the exploration of indirect operations in patients suffering from mitral stenosis. In general these have been attempts at palliation. These are reviewed to indicate their place in the evolution of present therapy and their relation to the current therapeutic armamentarium.

Cardiac Denervation

This has been carried out through low cervical incisions similar to those used in phrenic interruptions. The operation itself is not technically difficult. It consists of bilateral cervicodorsal sympathectomy with the removal of ganglions C-7, D-1, D-2, D-3, and sometimes D-4 and D-5. This has been carried out in an effort to reduce the mean heart rate. It has already been emphasized in previous publications[2, 3] that tachycardia is poorly borne by the patient with mitral stenosis. In this case, it should be to the patient's advantage to have episodes of tachycardia reduced in number and severity. At least theoretically this might be done by removing some of the cardiac accelerator pathways.

This operation has been performed twice in this series for patients with mitral stenosis. One patient who had had recurrent pulmonary edema every four to seven weeks for two years had no attacks for 12 months following

the operation. However, the patient was readmitted at the end of a year and died in pulmonary edema. The other patient had some control of her pulmonary edema for four months. She was then readmitted to the hospital with what was probably a pulmonary infarction and associated pulmonary edema. She did not recover. It is interesting, however, that this patient had objective evidence of reduced tendency to ventricular extrasystole following this denervation.

It was recognized that this was but a palliative procedure. Some of the objectives were attained, but the results make it apparent that this therapy is not adequate.

Interauricular Septal Defects

It has long been felt that patients with Lutembacher's syndrome tolerated mitral stenosis far better than patients with mitral stenosis alone. If this be true, and there is some statistical evidence to support this contention, it might be well to create an interauricular septal defect. It is rational that such patients should tolerate a mild degree of mitral stenosis better than those without the interauricular septal defect, because transient periods of pulmonary hypertension might be decompressed into the systemic circuit. Admittedly, such a therapeutic maneuver would be palliative, for people with Lutembacher's syndrome die at an average age that is far from acceptable as a therapeutic goal.

A possible place for the creation of interauricular septal defects has been mentioned.[2] This operation was performed on two patients. There was some brief beneficial effect. At the end of two to four months these patients ceased to enjoy continued palliation, and both have now had relief through finger-fracture valvuloplasty.

It must be assumed that this technic of creating interauricular septal defects is not so satisfactory as that described by Blalock.[4] However, the creation of Lutembacher's syndrome does not seem justified now that the results of finger-fracture valvuloplasty are so satisfactory.

The Bland-Sweet Anastomosis of Inferior Pulmonary Vein to the Azygos Vein[5]

This ingenious operation has as its objective the creation of a physiologic interauricular septal defect. Bland[6] comments on the 14 patients operated as follows: "The later course of this group has been of special interest. Fully half have had striking and continued relief from pulmonary edema, several were much benefited for one or two years but are now beginning to have milder recurrences of their previous trouble, a few had only questionable benefit, and three succumbed within a few days of the procedure.

"As was emphasized originally by the authors, the procedure is a compromise and not a cure. It was designed only for those with relatively strong small hearts as a protection to the lungs. These purely palliative procedures of the past three years have now been overshadowed and quite properly replaced by the more promising direct attack upon the mitral valve. The remarkable improvement in technique and consequent lessening in the risk of the intracardiac approach have rendered other methods less attractive and somewhat obsolete, but nevertheless useful, perhaps, under special circumstances where complicating aortic valve disease (regurgitation) places an added strain upon the left ventricle."

The Reservoir-Shunt Operation

In the period of consideration of indirect methods for palliating the symptoms of patients suffering from mitral stenosis, we were intrigued by the apparent improvement of some of the patients described by Bland and Sweet. They have created the physiologic interauricular septal defect described in the previous paragraph through the anastomosis of the superior division of the right inferior pulmonary vein to the proximal end of the divided azygos vein. From this procedure we developed our "reservoir-shunt" operation, and this operation was performed twice. The rationale for this procedure was based on two assumptions. First, that the patients were improved by the operation of Bland and Sweet; and secondly, that the anastomosis usually closed. The assumption of improvement

was taken from the observations of the proponents of the operation. The second assumption, that the anastomosis closed, was derived from three facts: (a) 3 mm. and 4 mm. Blakemore tube anastomoses such as were used often close even when used in a site of favorable pressure gradients such as the femoral artery, (b) autopsy examination after two of these operations indicated that the anastomoses were closed, and finally, (c) superior vena caval catheterization failed to demonstrate patency of the anastomosis.

This apparent paradox of improvement in spite of closure of the anastomoses can be explained theoretically as foliows: A closed anastomosis is in effect ligation of the azygos vein and ligation of the superior division of the right inferior pulmonary vein. This might have salutary effect in a patient with mitral stenosis in one or all of three ways. First, ligation of the azygos vein might produce trapping of the systemic blood in the "mediastinal venous swamp" during periods of increased blood flow. This would amount to a peripheral venesection. Second, ligation of the superior division of the inferior pulmonary vein might be followed by trapping or reservoir action in the lesser circuit during periods of increased flow similar to a pulmonic venesection. Third, after ligation of the pulmonary vein the regional bronchial veins would enlarge to carry off the blood from the interrupted portions of the pulmonary venous circuit. These bronchial veins drain into the azygos system, and therefore, in effect, the shunt that was initially intended by the pulmonary to azygos vein anastomosis is actually accomplished in another way. In this way, it seemed possible that simple ligation of these two veins might exert a salutary effect in patients suffering from the effects of periodic increase in the pulmonary hypertension of mitral stenosis. Two such "reservoir-shunt" operations were performed; that is, simple ligation of the superior division of the right inferior pulmonary vein and the azygos vein. Both patients seemed to enjoy transient improvement. The improvement was not sufficient to control the symptoms of the disease and no improved circulatory dynamics could be demonstrated by cardiac catheterization. Both patients were offered finger-fracture valvuloplasty. One patient succumbed in pulmonary edema before she came to the direct operation; the other has since had relief of her stenosis through valvuloplasty.

The "reservoir-shunt" procedures represented an interesting physiologic experiment. They were expected to be palliative at best. The procedures seemed reasonable and far simpler than the azygos to pulmonary vein anastomosis of Bland and Sweet. However, there is no evidence that they offered any substantial relief as contrasted with the direct operation of finger-fracture valvuloplasty.

Present Valvuloplasty and its Deficiencies

The technic of finger-fracture valvuloplasty has been described in detail elsewhere.[1] It consists of blunt dissection of the fusion bridges with the finger (fig. 5) and is possible in the vast majority of the patients. In some type II forms of mitral stenosis (approximately 10 per cent of all patients), it is necessary to use instruments for incision[1] somewhat similar to Bailey's valvulotomes. Usually, however, we use a blade that takes advantage of the finger-fracture blunt dissection technic (fig. 6).

The finger-fracture valvuloplasty technic is preferred to valvulotomy or commissurotomy for four reasons. *First*, delicate digital exploration of the stenotic orifice and of the leaflets is difficult when encumbered by an instrument. *Second*, incision through large calcific vegetations is both difficult and dangerous because of the possibility of dislodging emboli from the vegetations or because of thrombosis incident to crushing. Conversely, blunt finger dissection around such vegetations is simpler and safer. *Third*, hook knives and hook guillotines pick up chordae tendineae on the under side of the leaflets and more regurgitation may be produced. Therefore, when a necessity for incision arises in our work, we use a valvulotome that combines a cutting edge with finger-fracture (fig. 6). If a more powerful instrument is required, a modified punch is also available (fig. 7). *Fourth*, the hazards and complications

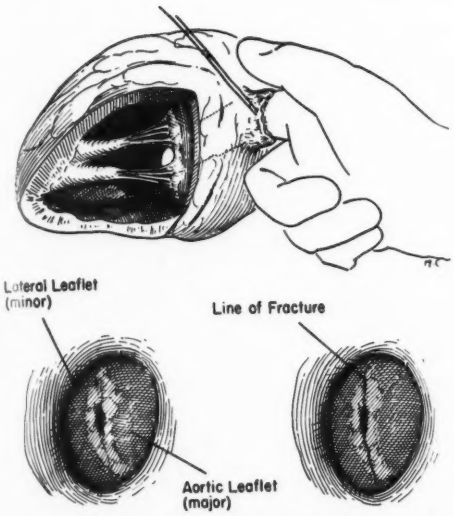

FIG. 5. *Above:* The operative index finger, introduced through the left auricle, in position to fracture the anterior and posterior fusion bridges. *Below:* Type I mitral stenosis before and after finger-fracture valvuloplasty of the anterior and posterior fusion bridges.

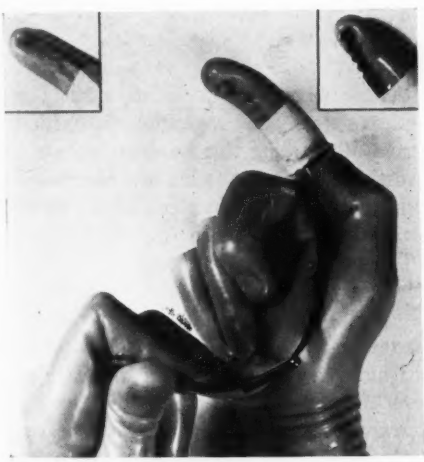

FIG. 6. Double-edged valvulotome. The blade is recessed into the soft tissues of the index finger for introduction into the left auricle. Insert upper left: Blade rotated 90° anteriorly for anterior fusion bridge incision and fracture. Insert upper right: Blade rotated 90° posteriorly for posterior fusion bridge incision and fracture. After the fracture is started with the valvulotome, it is further tailored to the annulus by blunt dissection with the finger, exercising care to avoid damage to the chordae tendineae.

of insertion of the finger into the auricle are greater in the presence of thrombosed and contracted auricular appendages or of laminated intra-auricular clots. Such hazards and difficulties as exist with the finger insertion alone are greatly augmented by addition of an encumbering instrument. When there is no auricular appendage and the surgeon needs to enter the heart by way of the superior pulmonary vein, it may be very difficult to thread a rigid instrument around such a curved course safely. These unfavorable situations tend to occur more frequently in the sicker and older patients.

FIG. 7. Guillotine valvulotome: A guarded reverse-action valvulotome for initiating fusion bridge fracture that is extended to the annulus by blunt finger dissection.

At times, the result of finger-fracture valvuloplasty feels to the surgeon like a nearly perfect restoration. Although this is unusual in advanced disease, nevertheless clinical and laboratory evidence often indicates that marked improvement has occurred. If one considers the

closing mechanism of the normal leaflets and compares it to that of a moderately to markedly diseased stenotic orifice that has had valvuloplastic correction, he realizes that quite a different type of closing mechanism has been brought about. The normal leaflets close like parachutes that are placed in juxtaposition. The closure is secured by a broad surface of leaflet contact and overlap. The papillary muscle and chordae tendineae anchor the margins, then tighten the closure. Valvuloplasty in advanced disease brings about a simple flutter-valve mechanism. This simpler valve is generally competent and entirely adequate for normal intraventricular pressures. It is less likely to stand high intraventricular pressures such as occur with aortic stenosis, insufficiency or even hypertensive heart disease. This shortcoming of a flutter-valve is, of course, exaggerated when the chordae are markedly shortened and thickened. It is particularly difficult to produce a good flutter-valve when the chordae of the major and the minor leaflets are fused together in continuity with the elastic, flexible fish-mouth, such as is occasionally seen in type II pathology (fig. 3). When this situation is encountered, it is necessary at times to resort to the compromise of producing selective insufficiency, that is, incision or fracture in the ventricular leaflet. This compromise relief of stenosis seems most successful if the incision or fracture is well forward and lateral to the anterior group of chordae tendineae. Unfortunately, there is no method at the present time for anticipating or differentiating type I from type II stenosis before operation. Fortunately, the incidence of type II is something under 15 per cent. Those valves in which the stenosis is not significantly improved by the current surgical approach constitute less than 5 per cent. Progress is being made and this situation will not exist indefinitely.

Valvuloplasty is highly successful in dealing with the anterior fusion bridge in the type I process but it is not always as satisfactory in dealing with the posterior rolled edge or shelf. We may find that multiple incisions of the shelf and even the division of some chordae will be our eventual solution to this problem. At present, the results are good in this group but they may be improved. In type II stenosis considerable improvement in present operative technic is needed.

The place for prosthetic valves in the surgery of mitral stenosis and insufficiency has not been defined. Several interesting possibilities are being explored. Progress is being made experimentally in reducing the diameter of the annulus by excision of an anterior section of the ring. It may be possible to reduce the annulus with sutures. Perhaps eventually a combination of plastic valve and surgery in the annulus and deformed leaflets will prove useful.

Ancillary Problems in the Operating Room

The problems of anesthesia are very great in some patients with high pulmonary vascular pressures and in those with liver and myocardial damage. The respiratory assistor developed by Derrick, Maloney and Whittenberger[7] has been of great value in dealing with people in delicate cardiorespiratory balance. Even so, anesthesia with its concomitant muscular relaxation and peripheral vasodilatation in the patient who has a fixed or falling cardiac output renders hypotension a grave problem. Various means of avoiding this hypotension are being investigated. Drugs such as norepinephrine and Neosynephrine, mechanical adjuncts and intra-arterial transfusion (fig. 8)* are helpful.

The problem of preventing or dealing with pulmonary edema is inextricably tied up with the problem of avoiding tachycardia. The dangers of tachycardia and the mechanisms by which they contribute to pulmonary edema have been stressed elsewhere.[3] The control of excessive ventricular irritability and prevention of fibrillation are improving. In the operating room Prostigmin, 0.25 mg. given intravenously, has been used effectively in reducing rapid rates of various types.

The place for the extracorporeal pump and its field of usefulness will not be elaborated here.

* We are indebted to Dr. Carl Walter for the development of a simple method for the rapid transfusion of blood intra-arterially.

Gibbon, Dennis, Bjork, Clowes, Welch, Hapgood and others are making noteworthy progress. Contributions from this direction may become a reality within the near future.

The danger of embolic phenomena remains great. Early in our experience (first 30 patients), four patients died from emboli. Recently, there have been no deaths, although two minor accidents have occurred. In short, the problem has not been eliminated but it seems to be far less menacing than it was originally. Three changes in technic are unquestionably associated with this improvement. *First*, when clot is encountered in the appendage and

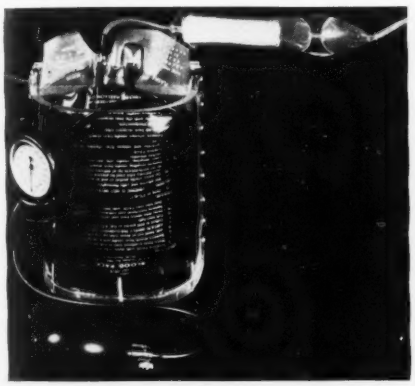

FIG. 8. Intra-arterial transfusion equipment. The blood is contained in a flexible plastic bag that can be exhausted forcibly in the lucite container to deliver blood under regulated pressure.

auricle, no effort is made to shell out large and extensive cast thrombi. Rather, the finger is insinuated gently along the side of the clot toward the superior vein and thence into the chamber of the auricle without dislodging the clot. *Second*, during the period of greatest danger of embolization, that is, when the finger is in the auricle, the anesthesiologist presses on the patient's carotid arteries. This reduces the stream of blood up the carotids and reduces the flow down to the *aortic takeoff; thus the likelihood of cerebral accident* is reduced. *Third*, patients in whom there is extensive intra-auricular clot at operation are heparinized. This is started eight hours after surgery and continued for five days.

THE LIFE CYCLE OF PATIENTS WITH MITRAL STENOSIS

It is well known that patients with mitral stenosis have a clear-cut history of a previous rheumatic infection in only about one-half of the cases. Looking at it from a somewhat different point of view, if patients are followed from the time they first have their active rheumatic carditis, it has been shown by Walsh, Bland and Jones[8] to take at least 5 to 15 years before fully developed clinical signs of mitral stenosis are present. It is not known what circumstances determine the evolution of the stenosing process, whether it is the repeated insults of a continuing, active, rheumatic process or whether it is due chiefly to the contracture of the scarred valve margins, or both. This of course, has a bearing on the surgical results of operated cases. Because of this time interval, comparatively few patients in the first two or even the first half of the third decade of life, present themselves with clear indications for surgical intervention. Furthermore, the possibility of active rheumatic carditis is greatest in this younger age group.

Although in many patients mitral stenosis runs a comparatively benign course, most patients ultimately die from the effects of their disease. In the same study it was found that heart failure of one type or another accounted for 44 per cent of the deaths; in an additional 33 per cent, acute events in the peripheral circulation (mainly embolic) produced death. Pulmonary infarctions resulted in 11 per cent of the deaths. It can be seen, therefore, that the circulatory breakdown in patients with mitral stenosis occurs in differing fashions. In a good many patients the valvular obstruction apparently does not interfere significantly with effective circulation and this seems to be true even in the presence of a fairly high degree of stenosis in many patients. These patients run a course into the later age groups and die of congestive failure or peripheral vascular accidents, though some patients succumb to associated hypertension or degenerative vascular disease.

In another and younger group, active rheumatic infection dominates the picture. In our

series of pathologic cases studied post mortem, active rheumatic infection was found to be a significant factor in determining death in only one of 100 patients. Many patients develop and still die of the consequences of bacterial endocarditis. During the years 1945–1949, after the advent of penicillin, the incidence of death occurring in patients who had or had recently had subacute bacterial endocarditis was exactly the same (8 per cent[9]) as in a group of patients studied 20 years before at the same hospital by Davis and Weiss.[10]

There is a final group, and this is a group with which we are particularly concerned in the surgery of mitral stenosis. These are patients who usually have increasing pulmonary difficulty that can be explained largely on a mechanical basis due to the elevated pressure in the pulmonary capillaries leading to edema. This disability may be chronic dyspnea or it may be punctuated by acute attacks of violent dyspnea or pulmonary edema, hemoptysis, cough, wheezing, and frequently by a sense of fatigue and a tendency to lose weight. The deterioration of these patients may be steady and slow, but it frequently increases rapidly. Although slight edema may be present in these patients and many of them do get relief of dyspnea from sodium depleting regimens, true right-sided failure has not yet developed. They may or may not fibrillate but, particularly if they are in auricular fibrillation, the possibility of peripheral emboli occurring at any time is very real. Their disability is severe and increasing, the prognosis under medical management is hazardous, and since their symptoms stem back directly to the obstruction of the mitral valve, the prospect of relief from surgery in these cases is excellent.

The final phase in this group of patients with mitral stenosis is when pulmonary vascular changes become severe. It is then that the right ventricle fails, massive edema occurs with chronically enlarged livers, and elevated venous pressure is present. Pulmonary symptoms may or may not be somewhat alleviated at this point. There frequently is an apparent diminution in pulmonary symptoms, due in part to lessened activity on the part of the patient and in part to the protection of the pulmonary capillaries by the high resistance to blood flow through the arterioles and small arteries. Pulmonary infarctions, however, are common. Most of the patients are in auricular fibrillation. Functional tricuspid insufficiency may develop. These patients are chronic invalids. Since the disease has progressed so far, the prospect of significant improvement by operation is not so good as in the former group; the risk of operation is very much greater.

There is, unfortunately, no simple way of selecting patients who are suitable candidates for operation because of the progression of their disease other than by a complete evaluation of the clinical picture. Objective studies such as by cardiac catheterization are helpful, and in obscure cases occasionally necessary. When pulmonary vascular changes are advanced, the diagnosis can usually be made roentgenographically by a demonstration of large right ventricle and pulmonary artery.

A word is in order in regard to pulmonary vascular changes. It is well known, as demonstrated by Parker and Weiss[11] and by Larrabee, Parker and Edwards,[12] that organic changes of the nature of pulmonary arterial and arteriolar sclerosis, as well as intra-alveolar fibrosis and edema, may occur in patients with high-grade mitral stenosis. In our clinicopathologic study we were not able to demonstrate, however, a close correlation between the degree of mitral stenosis and the degree of such changes other than the fact that such organic changes are unlikely to be present without well-marked mitral stenosis. However, the reverse is not true; severe mitral stenosis may exist with little or no pulmonary vascular change. From a clinical, physiologic and pathologic study that has also been made by one of us,[13] it is evident that some patients tolerate high-grade pulmonary changes with comparatively few symptoms. Since pulmonary changes occur with such frequency in patients with chronic high-grade mitral stenosis with symptoms, it is almost certain that many of the patients who have been successfully operated upon have had such changes. The almost uniform marked relief of symptoms in these patients suggests that such organic changes either do not produce the symptoms or are to some extent

reversible. It has been demonstrated in a small group of patients that high degrees of pulmonary resistance regress to or nearly to normal six months to a year after surgery. At the present time, therefore, the fear that such organic changes may persist in a given patient seems doubtful and their presence is no contraindication to operation.

Clinical Classification of Patients Suffering from Mitral Stenosis

It is very difficult to present, for such a protean disease, an accurate and sound clinical classification suitable for use in selecting patients for operation. A working classification useful in the light of our present knowledge is as follows:

Group I comprises patients whose present course is *benign*. They have auscultatory signs of mitral stenosis but few, if any, symptoms and minimal evidence of increase in pulmonary vascular pressure. Patients in this group may continue to run a benign course or they may develop an acceleration of their illness which shifts them to one of the other groups.

Group II includes patients somewhat *handicapped* by a static degree of moderate dyspnea on effort or by rare attacks of acute dyspnea or other pulmonary symptoms provoked by an extrinsic cause such as unusual exertion, fatigue or by severe infection. Rarely they may have some peripheral edema but do not have evidence of frank right ventricular failure.

Group III includes patients whose disability is *progressive rather* than static. There may be increasing dyspnea on effort or easily provoked attacks of hemoptysis, chest pain and pulmonary edema. They may suffer from palpitation, tachycardia, and distress over the liver on exertion. At any time they may slip into group IV or may die in an acute attack of pulmonary edema or from peripheral or pulmonary infarction. Their life expectancy under medical therapy is *hazardous*.

Group IV is a *terminal* group. They are completely incapacitated, usually with right ventricular failure manifested by chronically elevated venous pressure, considerably enlarged liver, and a marked tendency to congestion. Their pulmonary disability may or may not be greater than those in group III. They often have poor liver function, even ascites, evidence of decreased peripheral blood flow, and many have had emboli. Most of them are in auricular fibrillation.

Certain additional factors of importance in evaluating patients for operation are not included in this classification. As these jeopardize good results from surgery, they constitute *relative* contraindications.

1. Clinically, obvious active *rheumatic carditis* is a contraindication to surgical intervention. This position is taken because, in general, the degree of eventual residual clinical handicap is difficult to assess in the presence of active carditis.The patient may not require surgical intervention. Also, the effect of surgical intervention and valvuloplasty on the active disease as well as the effect of the active disease on the valvuloplasty have not been clarified. These questions will be answered in the course of time since acute carditis is occasionally found unexpectedly at operation.

2. *Severe aortic valvular disease* sufficient to produce peripheral signs of aortic regurgitation or a definite enlargement of the left ventricle, due either to aortic regurgitation or to aortic stenosis, contraindicates the operation. It has been pointed out that severe aortic disease sufficient to cause left ventricular hypertension places an extra burden on the surgically created mitral flutter-valve. Recently, however, valvuloplasty has been done in the presence of mild aortic valvular involvement. In this connection, it should be noted that patients who are considered for operation frequently have a blowing diastolic murmur of slight to moderate intensity heard along the left border of the sternum. This may be due to functional pulmonic regurgitation (Graham-Steell murmur). The presence of such a murmur does not contraindicate operation providing the diastolic blood pressure at rest is greater than 50 mm. Hg.

3. *Mitral regurgitation* is a relative contraindication to operation. This is difficult to quantitate. The intensity of the systolic murmur at the apex is not a good guide. Very loud, high-pitched, musical murmurs are much more likely to accompany severe mitral regurgitation. Easy fatigability is a more prominent symptom than dyspnea. When there is enormous dilatation of the left auricle, mitral regurgitation of significant degree is likely to be present. This has been pointed out by others.[14, 15] Auricular fibrillation is nearly always present. The presence of enlargement of the left ventricle in the absence of aortic disease or hypertension suggests the possibility of mitral regurgitation. Minor degrees of left ventricular enlargement are difficult to assess roentgenologically in the presence of a very large right ventricle. The electrocardiogram is more helpful than the roentgenogram in this connection. Marked pulsation of the left auricle also suggests such a diagnosis, but it is by no means an infallible sign. The presence of a so-called "insufficiency" curve[16] in the pulmonary "capillary" pressure tracing obtained by cardiac catheterization is suggestive of significant mitral regurgitation. Such curves are not readily obtained, however, and their

interpretation is not simple. There may be a startling discrepancy between the clinician's impression of the degree of regurgitation and that of the surgeon as he palpates the fish-mouth funnel at the operating table. The surgeon too may gain an erroneous impression. For example, a low intraventricular pressure at the time of operation produces little or no palpable regurgitant jet; on the other hand, a feeble regurgitant jet could be due to a very large ostium. Either would give the surgeon the impression of minor insufficiency. It is important to develop accurate criteria for estimating mitral regurgitation for the present state of surgical correction of mitral regurgitation of major degree is not satisfactory. *The patient who has a major degree of insufficiency but who is clinically stable should not have surgery now. All of the above clinical aids must be combined* to make this quantitative estimate.

4. *Auricular fibrillation* or the history of definite *peripheral emboli* do not contraindicate operation. More than 60 per cent of our patients have been fibrillators. However, they probably make the immediate hazard of operation greater and the possibility of a peripheral embolus being dislodged at the time of operation somewhat more likely. We have encountered eight peripheral emboli occurring either at the time of operation or within 24 hours thereafter. Six of these patients were in auricular fibrillation at the time of operation and six had been in chronic congestive failure.

5. *Extensive valvular calcification* has never deterred us from carrying out valvuloplasty but it must be construed as an additional hazard. The first hazard is in relation to clot forming on such leaflets after they have been mobilized and the second factor is that such leaflets often are quite difficult to mobilize perfectly. The bases of such leaflets are always flexible but clumsy; bulbous calcific margins do not swing open and shut freely.

6. *Advanced age* obviously is associated with certain variations in the physical state that influence the surgical risk and result. Older patients have, in general, had their disease longer, the incidence of intra-auricular clot is higher and their recuperative power is less. While the most dramatic rehabilitation occurred in one 55 year old man bedridden for 18 months and in constant edema and congestive failure, age above 50 requires special attention. Those between 30 and 40 have done best. There have been only five patients under 30. They have all done well.

7. *Organic tricuspid stenosis* may make the operation more hazardous and the surgical result less favorable. Clinical evaluation of stenosis and insufficiency is difficult. Cardiac catheterization may be helpful in making this distinction.

8. *Associated disease* such as arteriosclerosis, hypertensive cardiovascular disease, asthma or other complicating and debilitating states are obviously important. These are of infinite variety and merely mean that after consideration of all factors the good clinician must add "his clinical impression" for or against the decision to intervene.

In a sense this classification constitutes a definition of some contraindications and indications for surgery. Group I patients do not need surgery and therefore this state constitutes a contraindication. Group II disability may justify waiting for improved surgery because the illness is static but if that static disability is unacceptable to the patient, it may constitute a reasonable justification for surgical intervention. To date, we have not felt that these patients should have operation now.

Those patients in group III are the ideal candidates for surgery now as the prognosis without intervention is bad and the risk of valvuloplasty is low (less than 10 per cent) considering the severity of the disease. The high mortality rate in group IV (less than 40 per cent) will be shown to be less hazardous to the patient than his disease at that phase of the life cycle; therefore, this terminal state does not contraindicate surgery. However, it argues strongly for prophylaxis in the form of surgery before this condition develops.

Detailed postoperative results as regards objective changes including blood flow, pulmonary pressures, pulmonary function and clinical condition will be reported separately.

It should be stated, however, that patients in group III have all been markedly improved and all have maintained or increased their degree of improvement over the period of observation (up to three years). It is common in this group of patients, who were seriously limited to stair climbing with difficulty or even to essential bed and chair existence before operation, to skate, ski, bicycle or dance after operation. (Rehabilitation in skating or dancing returns earlier than full housework for understandable reasons.)

The degree of improvement in most of the patients in group IV has been much less though it is often dramatic. Most have been able to resume sedentary occupations or light housework and have required infrequent or even no further mercurial diuretics. In no instance has a patient who survived operation had poorer cardiac function.

The Present Responsibility

Certain patients can be selected whose present course is benign (group I) but who of course may degenerate to one of the more serious categories at any time. If properly followed and observed, these patients should not have surgical intervention at this time. Some of these patients will never require surgical intervention. Furthermore, there is a real possibility that surgery can render this group a substantial disservice (a) incident to the risk and discomfort of an unnecessary operation, (b) incident to the valvular alteration itself, and (c) incident to the sacrifice of the auricular appendage in the event that subsequent operation should become necessary.

In group II, patients whose degree of disability is static, selection of cases for operation must be made on the basis of the discomfort and limitation in the individual case. The risk of operation in this group is not great; it can be carried below 5 per cent. The chance of relieving the handicap is good. On the other hand, if patients in this group are not materially discommoded by their illness, it is entirely possible that better valvuloplasty may be available within the next year or so. We have deferred surgery in this group, placing the patients on a waiting list and meanwhile insisting on careful clinical check lest they slip into group III.

Group III. The risk in this group is relatively low, below 10 per cent in this series, whereas the benefits are considerable. These patients are usually restored to comfortable, useful lives. This is because they get good, functional valvuloplasty before there is irreversible damage in the lung, myocardium and liver. In short, they are treated before they have slipped into group IV or die. These patients in group III *constitute the ideal and urgent candidates for surgery at this time.* They represent the most serious responsibility of the cardiologist in protecting the patient against fatal issue that is possible at any time while in this group or before he undergoes further progression into group IV. In our 48 patients of group III, there have been but four deaths.

Group IV. This, like group II, again represents a borderline group but in quite another way. These patients are suffering from a malignant disease. During the early phases of this study we preferred to take our surgical candidates from the group of dying patients. A control group demonstrates how group IV patients fared without surgical intervention. The control group constituted patients in group IV acceptable for surgery but who did not have it for various reasons, such as refusal of surgery on the part of the patient or the patient's family. There were 19 of these patients and 17 died within one year, 15 within six months. Thus, it becomes apparent that it is fair to call this a terminal or malignant phase. There were 39 patients in group IV who were operated on and 14 died from this intervention.* Of course, these results are far better than those in the control group and if we were discussing carcinoma of the stomach or liver we would be delighted with such salvage rates. However, in this malignant phase the results are being improved.

It becomes apparent that we must continue to explore the degree of usefulness of a technic established as beneficial in some instances until we clearly define the limitations of the method. At the same time, we are trying to improve the method and therefore the benefits of surgery in group IV. These efforts at improving the surgery of the terminal stage must continue until the physician accepts his responsibility consistently in earlier phases of the disease. The difference in mortality that patients face between group III and group IV is not inconsiderably a responsibility of the physician.

The classification of patients as to severity of disease and evaluation of patients as surgical risks still has not been reduced to a mathematical formula embracing all variables, in spite of our efforts. These equations remain only as good as the man applying the measure. The authors frequently find themselves in disagreement concerning classification of their patients.

* Three additional patients have died from other causes, subsequently.

Summary

An attempt is made to define the physician's responsibility in the selection of patients for the surgical treatment of mitral stenosis.

The anatomy of the normal mitral valve is discussed. A classification of the morphologic types of mitral stenosis is presented. The evolution and present position of finger-fracture valvuloplasty are outlined in the light of other indirect and direct methods of surgical treatment. The life cycle or clinical course of patients suffering from mitral stenosis is discussed, and a clinical classification of such patients is presented. These patients are divided into four groups:

Group I. *Benign* (murmur without handicap).

Group II. *Handicapped* (nonprogressive).

Group III. *Hazardous* (progressive).

Group IV. *Terminal.*

It is felt that surgical intervention is justified in group IV because it presents a salvage rate of better than two-thirds of the patients, in contrast to a mortality rate of approximately 90 per cent without surgery. Unfortunately, irreversible changes in lung, liver and myocardium prevent maximum recovery in this group although they run the highest mortality risk.

Group II patients, the *handicapped*, may now be operated or not depending on the degree of disability. Presumably surgical technics will improve and patients who have minimal handicap that is well borne and stable could reasonably be advised to wait for further technical improvements. On the other hand, good surgical treatment is now available and group II patients with marked handicap can be offered relief at the present time.

Group III patients are considered urgent indications for surgery now, inasmuch as their course under medical treatment is *hazardous* and their rehabilitation through surgery is excellent and in some cases even dramatic. The surgical mortality in this group is less than 8 per cent.

REFERENCES

[1] Harken, D. E., Dexter, L., Ellis, L. B., Farrand, R. E., and Dickson, J. F., III: The surgery of mitral stenosis. III. Finger-fracture valvuloplasty. Ann. Surg. In press.

[2] —, Ellis, L. B., Ware, P. F., and Norman, L. R.: The surgical treatment of mitral stenosis. New England J. Med. **239:** 801, 1948.

[3] Ellis, L. B., and Harken, D. E.: Mitral stenosis; clinico-physiologic correlations, with particular reference to surgical intervention. Tr. Am. Clin. & Climatol. A. **60:** 59, 1949.

[4] Blalock, A., and Hanlon, C. R.: Interauricular septal defect. Its experimental production under direct vision without interruption of circulation. Surg., Gynec. & Obst. **87:** 183, 1948.

[5] Bland, E. F., and Sweet, R. H.: A venous shunt for marked mitral stenosis. Tr. Am. Clin. & Climatol. A. **60:** 71, 1949.

[6] Bland, E. F. Personal Communication.

[7] Maloney, J. V., Derrick, W. S., and Whittenberger, J. L.: A device producing regulated assisted respirations; its effect on hypoventilation in thoracic surgery. In Proc. Am. Coll. Surg. Philadelphia, Saunders, 1950.

[8] Walsh, B. J., Bland, E. F., and Jones, T. D.: Pure mitral stenosis in young persons. Arch. Int. Med. **65:** 321, 1940.

[9] Ellis, L. B., Bloomfield, R. A., Graham, G. K., Greenberg, D. J., Hultgren, H. N., Kraus, H., Maresh, G., Mebane, J. G., Pfeiffer, P. H., Selverstone, L. A., and Taylor, J. A.: Studies in mitral stenosis. I. A correlation of physiologic and clinical findings. Arch. Med. In press.

[10] Davis, D., and Weiss, S.: Rheumatic heart disease. I. Incidence and role in the causation of death. A study of 5,215 consecutive necropsies. Am. Heart J. **7:** 146, 1931.

[11] Parker, F., Jr., and Weiss, S.: The nature and significance of the structural changes in the lungs in mitral stenosis. Am. J. Path. **12:** 573, 1936.

[12] Larabee, W. F., Parker, R. L., and Edwards, J. E.: Pathology of intrapulmonary arteries and arterioles in mitral stenosis. Proc. Staff Meet., Mayo Clin. **24:** 316, 1949.

[13] Graham, G. K., Taylor, J. A., Ellis, L. B., Greenberg, D. J., and Robbins, S. L.: Studies in mitral stenosis. II. A correlation of postmortem findings with the clinical course of the disease in 101 cases. Arch. Med. In press.

[14] Wood, P.: Discussion on management of rheumatic fever and its early complications; cardiac complications. Proc. Royal Soc. Med. **43:** 195, 1950.

[15] Parsonnet, A. E., Bernstein, A., and Martland, H. S.: Massive left auricle with special reference to its etiology and mechanism. Am. Heart J. **31:** 438, 1946.

[16] Gorlin, R., Haynes, F. W., Goodale, W. T., Sawyer, C. G., Dow, J. W., and Dexter, L.: Studies of the circulatory dynamics in mitral stenosis. II. Altered dynamics at rest. Am. Heart J. **41:** 30, 1951.

Alcohol Vapor by Inhalation in the Treatment of Acute Pulmonary Edema

By ALDO A. LUISADA, M.D., MORTON A. GOLDMANN, M.D., AND RUTH WEYL, M.D.

Accepted therapy of pulmonary edema is contraindicated in shock, central nervous system lesions, or pregnancy. Diagnosis of the underlying disease is not always immediately possible. Alcohol inhalation, previously tested in animals, changes surface tension of the foam and has beneficial effects. Clinical experience has revealed prompt relief in over one-half of the acute cases, definite improvement in another 29 per cent. Some cases with subacute edema also exhibited decreased foaming. The absence of contraindications and the possibility of using the method in conjunction with other procedures are favorable elements of alcohol therapy by inhalation.

NOTWITHSTANDING conventional therapy, mortality associated with acute pulmonary edema remains high. The need for other generally applicable methods of treatment is evident. In evaluating such new procedures, the following factors should be considered:

(a) *Possibility of Shock.* Several types of acute pulmonary edema occur in conditions where there is impending shock, whether cardiogenic (myocardial infarct, extreme bradycardia of A-V block) or peripheral (trauma, burns, certain cases of brain lesions). Among the accepted therapeutic procedures are the use of morphine,[1–3] phenobarbital and other barbiturates,[1–3] chloral hydrate,[1–3] spinal anesthesia,[4] venesection, mercurial diuretics, and positive pressure respiration.[5] One of the main effects of these procedures is to decrease venous return[6–9] which may be followed by irreversible shock.

(b) *Central Nervous System Lesion.* Other types of acute pulmonary edema are associated with injury to or lesions of the central nervous system (cerebral hemorrhage, thrombosis, or embolism; subarachnoid hemorrhage; poliomyelitis; tetanus; skull fracture). Anesthetics and sedatives are generally contraindicated because they may cause respiratory paralysis or shock.

(c) *Pregnancy.* Acute pulmonary edema may complicate pregnancy or labor. Large doses of morphine and mercurials might be detrimental to the fetus.

For these reasons, one of us studied a new approach based on the use of antifoaming agents by inhalation and demonstrated its favorable action in experimental pulmonary edema.[10, 11] The present study reports the first results of similar treatment in man.

PART I. METHODS OF CLINICAL ADMINISTRATION AND DETERMINATION OF TOLERATION OF ALCOHOL BY INHALATION

Before attempting to administer alcohol by inhalation to patients with acute pulmonary edema, it was necessary to determine the best method for use in man and to establish the toleration of this procedure by normal subjects and cardiac patients.

Procedure

Six normal subjects, two postoperative patients, and two cardiac patients were selected for this preliminary study. Blood tests for alcohol content in the blood serum before and after 30 minutes of alcohol inhalation* were done in two normal subjects. Blood pressure and pulse rate were determined in all subjects before starting the inhalation and every five minutes throughout the experiment. Reaction to stimuli was observed, and subjects were asked to state their subjective sensations at five minute intervals.

Method 1. Use was made of the standard equipment for gas anesthesia. The method of rebreathing with carbon dioxide absorption was used in order

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This study was performed under the tenure of a Teaching Grant of the National Heart Institute, U. S. Public Health Service, held by Dr. Luisada.

* Titration was made by using the potassium dichromate method according to Harger.[12]

to increase the alcohol concentration of the vapor. A wick-type vaporizer was filled with 95 per cent alcohol. Pure oxygen was administered first by bag and mask; then an increasing amount of alcohol vapor was given until the maximum capacity of the vaporizer was reached. The subjects inhaled the full concentration for about 30 minutes. The alcohol concentration thus reached was never found difficult to breath. It provoked coughing in only one person; one normal subject started to laugh. In all subjects it produced mild euphoria and slight drowsiness.

In the normal subjects, only insignificant changes in blood pressure and pulse rate were observed. In one, marked sinus arrhythmia was noted after five minutes, but subsided later. *Serum concentration of alcohol* was found to be less than 10 mg. per 100 cc. after 30 minutes.* The two cardiac patients, a 67 year old man with coronary heart disease and heart failure, and a 62 year old woman with hypertensive heart disease and heart failure, had been previously digitalized. Their tolerance of alcohol inhalation was good. The blood pressure rose from 160/85 to 180/95 in one case, and persisted unchanged in the other. Their pulse rates did not change. Both stated that they were feeling "better" after the inhalation.

Method 2. In order to devise a simpler and safe standard technic for routine use, another method was employed in other experiments. The device consisted of an oxygen tank, a two-stage adjustable pressure regulator, a Bourdon-type flowmeter, a positive pressure mask, and a special type of vaporizer. The vaporizer used (Model 15, Ohio Heidbrink Humidifier) utilizes the principle of jet atomization to make a gas into a fog which is further bubbled through several inches of fluid (in this case, alcohol) for increased saturation. In the course of our experiments, it soon became evident that *30 per cent alcohol* in the vaporizer should be used with the meter mask. In order to achieve about 100 per cent oxygen concentration, a flow of oxygen of 10 to 12 liters per minute is necessary for the average person. Collapse of the collecting bag at the end of inspiration indicates need of higher oxygen flow. The flow of oxygen through the alcohol should be started slowly (about 3 liters per minute) in order to obtain a slight local anesthesia before higher concentrations can be tolerated. By slowly increasing the rate, a 10 liter flow was well tolerated at the end of about five minutes. It should be kept in mind that the amount of alcohol vaporized increases with the flow of oxygen.

In healthy adults studied with method 2, essentially the same results were observed as in the previous series, namely, slight euphoria and slight changes of pulse and blood pressure: slight increase of blood pressure (10 to 20 mm. systolic) during the inhalation, slight decrease after removal of the mask.

Method 3. Some patients with pulmonary edema do not tolerate a mask for any length of time because of cough and expectoration, or a smothering feeling. For these patients, an alternate method was devised during the course of the therapeutic experiment. The pressure gage, flowmeter and vaporizer all the same as described in method 2. The vaporizer is filled to the appropriate level with *95 per cent alcohol;* a nasal catheter is placed into the nasopharynx and is then connected to the vaporizer. The flow is started at a rate of 2 to 3 liters per minute and then gradually increased to 7 or 8 liters per minute within three to five minutes, as tolerated by the patient. The patient should be instructed to avoid oral respiration.

Method 4. A technic of diffusing alcohol vapor into an open tent was discarded early in the therapeutic experiment because of discomfort to the patient.

Discussion

These four methods were studied in order to apply alcohol vapor inhalation to clinical cases of acute pulmonary edema. The desired effect is based on the antifoaming action of alcohol exerted locally in the air passages and not on any systemic effect. For this reason, finding that after 30 minutes of inhalation only an extremely small concentration of alcohol was present in the blood was accepted as favorable. Of the various methods, method 2 (mask) combines the effects of pressure breathing with those of alcohol therapy. On the other hand, method 3 (nasal catheter) permits the patient to expectorate; it fails to induce a feeling of suffocation; and has been found easier to use. Method 3 was used in most of the patients studied in part II of this report.

Conclusions of Part I

Alcohol vapor by inhalation is well tolerated by normal subjects and cardiac patients. Four methods have been studied. The two most practical are:

(a) One employing a nasal catheter.

(b) One making use of a positive pressure mask.

The concentration of alcohol detected in the blood was small; its general effects were negligible.

* According to Goodman and Gilman,[13] a blood concentration of alcohol of 100 mg. per 100 cc. is associated with intoxication in only about one fourth of the subjects.

Part II. Administration of Alcohol Vapor by Inhalation to Clinical Cases

Results

The results of our study are summarized in tables 1 and 2.* A total of 14 patients received alcohol treatment for 17 acute attacks of paroxysmal pulmonary edema. In addition, seven other patients with pulmonary edema of longer duration and not necessarily paroxysmal in nature also received treatment.

Classified according to primary etiologic condition, the diagnoses in the acute cases were as follows:

Hypertensive heart disease	10
also coronary heart disease	3
also pregnancy at term	1
also chronic glomerulonephritis and uremia	1
also coarctation of the aorta	1
others	4
Coronary heart disease (7 weeks after a myocardial infarct)	1
Rheumatic valvular disease	1
Various	2
Total	14

Seven of these attacks were very severe, while all others were severe. In three attacks (nos. 1, 8 and 13), the attending physicians declared that they "had never observed a more severe attack." Alcohol inhalation by nasal catheter was well tolerated by all patients, while inhalation by mask was refused by one.

The result of alcohol inhalation in the *acute and severe attacks* was as follows:

(a) The beneficial result was prompt and marked in 10 attacks (nos. 1, 2, 3, 4, 7, 8, 10, 11, 14, 17) or 58 per cent.

(b) There was definite improvement in five attacks (nos. 9, 12, 13, 15, 16) or 29 per cent.

(c) No improvement was noted in two attacks (nos. 5, 6) or 13 per cent, but in one of them the patient did not tolerate alcohol and in the other the patient objected to it at first and possibly received an inadequate dose.

(d) There was only one fatality (case 5). This patient died four hours after treatment was discontinued.

The seven cases of *pulmonary edema of long duration* were classified according to the following primary diagnoses:

Coronary occlusion	2
Heart failure (with coronary heart disease in one)	2
Postoperative complications	2
Pneumonia and anemia	1

Three of the attacks were severe, the other four of medium severity. Marked improvement was observed in one patient (case 4); moderate to slight improvement in two (cases 3 and 6); and doubtful result or no improvement in the other four. When improvement was noted, the sputum lost its foamy quality, becoming more liquid and more easily expelled. The general condition of all patients in this group was very poor to terminal when therapy was instituted.

Case Reports

The following clinical case reports have been selected as illustrative of the dramatic improvement which followed administration of alcohol vapor by inhalation.

Case 1. A woman of 72 years was suffering from hypertensive heart disease with cardiac enlargement and repeated episodes of paroxysmal nocturnal dyspnea. Her blood pressure varied between 150/80 and 180/110, with occasional further increases to 230/130; the latter usually followed by paroxysms of dyspnea or pulmonary edema. Several electrocardiograms, recorded during two years prior to admission, showed evidence of coronary insufficiency.

On Feb. 15, 1951, at 4:45 a.m., the patient experienced a severe choking sensation and started gasping for breath. Soon afterward, yellow-tinged foam poured repeatedly from the nostrils and mouth. The pulmotor squad, immediately called, started oxygen administration at once. An internist, who had been treating the patient, reached the patient's home at 5:30 and later described the attack as "the most severe observed in his life." Foam kept pouring from the nostrils and from the patient's mouth. The pulse was 120; the blood pressure, 170/100. Both lung fields presented diffuse and numerous rales of various caliber up to the gurgling of foam in the trachea. The patient was only partly conscious.

* At the request of the Editor tables 1 and 2 are being omitted. These tables will appear in reprints.

Within a few minutes after the physician arrived, the following medication was given: (a) Pantopon, 1 cc., subcutaneously; (b) aminophyllin, 0.25 Gm., intravenously; (c) Demerol, 100 mg., intravenously. Some degree of general sedation ensued, but the foamy expectoration continued unabated. The nose and pharynx of the patient were cleaned through suction, again without improvement.

At 7 a.m. (more than one hour after the last medication), a large gauze pad, soaked with 40 per cent alcohol was applied over the mouth and nose of the patient and covered with the oxygen mask so that the oxygen flow reached the respiratory passages after becoming surcharged with alcohol vapor. Within 10 minutes, foaming decreased and tracheal gurgle disappeared. At 7:15 a.m. the patient was comfortable and conscious; the number of rales over the lung fields had decreased remarkably. The oxygen mask was removed and the patient was sent to the hospital by ambulance. Upon arrival, only minimal traces of pulmonary edema were found, so that no further medication was considered necessary. The patient was sent home three days later.

The patient died six weeks later following thrombosis of the abdominal aorta and unsuccessful surgical intervention. An electrocardiogram, recorded a few hours before death, revealed a supraventricular tachycardia. No autopsy was obtained.

The impression of the internist concerning the effectiveness of alcohol treatment was so definite that he insisted in reporting the case, in spite of the unusual way by which alcohol had been administered as an emergency procedure. It is noteworthy that all drugs administered should have passed their peak of action long before administration of alcohol vapor.

Case 8. A 43 year old Negro woman was admitted to the hospital on Jan. 9, 1951, because of hypertension complicating pregnancy. A para XII, gravida XV, she offered no complaints. Hypertension had been noted during two earlier pregnancies; however, no interim examinations had been performed. Physical examination revealed an obese woman with blood pressure 230/140, pulse 84, temperature 98.6 F., and respirations 20. The size of the uterus was consistent with a nine month pregnancy. Fetal heart tones were heard at the rate of 152 per minute.

Laboratory findings on admission were: hemoglobin 50 per cent (7.8 Gm.), red blood cells 3,120,000, white blood cells 14,200; traces of acetone and protein in the urine; nonprotein nitrogen 19 mg. per 100 cc.); serum protein 5.7 Gm. per 100 cc. (albumin 3.1 Gm. per 100 cc., globulin 2.6 Gm. per 100 cc.); blood uric acid 6.1 mg. per 100 cc.; negative Kahn. The chest film was reported as being within normal limits. The electrocardiogram was interpreted as being within normal limits, with left axis shift.

Shortly after admission, the patient, considered to be a pre-eclamptic, was placed on a modified Stroganoff regime. This included the periodic use of morphine sulfate, magnesium sulfate, and 25 per cent dextrose in water parenterally, and ammonium chloride by mouth. By January 10, the patient's blood pressure dropped to 154/92 and the fetal heart tones could not be heard with certainty. At 1:15 p.m., spontaneous rupture of the fetal membranes was noted.

While lying supine upon a delivery table following sterile vaginal examination, the patient complained of flushing and a choking sensation. She became severely dyspneic, cyanotic, and developed acute pulmonary edema of the greatest severity. At 8:30 p.m., positive pressure oxygen by mask was instituted. Successively, morphine sulfate, 30 mg.; aminophyllin, 0.5 Gm.; atropine sulfate, 0.5 mg.; sodium amytal, 0.5 Gm.; and Digalen, 1 cat unit, were administered intravenously within 15 minutes after the onset. At 9:10 p.m. (40 minutes after these measures were completed), frothy sputum was still being emitted in copious quantity from the delirious patient's mouth.

Administration of alcohol-oxygen vapor according to method 2 was then started by mask, intermittently, under variable pressure and rate of oxygen flow. Improvement was prompt, dramatic and progressive. Within 15 minutes, the foam became more liquid in character so that more effective expectoration was possible. Within 20 minutes, the patient was no longer in severe distress. At the end of 30 minutes, the patient was able to sit up and speak clearly, although with some effort. Bubbling and crepitant pulmonary rales were markedly reduced in quantity. No further alcohol vapor was given. Approximately seven hours later, the patient spontaneously delivered a female infant who required resuscitation.

The patient was re-examined on January 15. Her blood pressure was 185/110 and the pulse, 82. The conjunctivae were pale. A grade 2 apical systolic murmur and grade 3 hypertensive retinopathy (Keith-Wagener) were present. Otherwise, the findings were noncontributory. Seven weeks post partum the patient's status was re-evaluated at the Cardiac Clinic. Although free of complaints, she was found to have a blood pressure of 230/120 and pulse of 88 in both arms; the apex was 4 cm. outside of the left midclavicular line, and a trace of pretibial edema was present. Fluoroscopy revealed left ventricular and probably also left auricular enlargement. A 12 lead electrocardiogram, including standard and unipolar extremity and chest leads, was interpreted as being abnormal and consistent with left ventricular hypertrophy and "strain." Final diagnosis was hypertensive cardiovascular disease and term pregnancy. The infant is free of illness, but somewhat retarded in growth and development.

In summary, this 43 year old woman with asymptomatic hypertensive cardiovascular disease and

term pregnancy developed acute paroxysmal pulmonary edema of the utmost severity. After an unsuccessful trial of conventional forms of medical therapy, oxygen-alcohol vapor was administered and was followed by prompt and dramatic recovery.

Case 14. A 58 year old Negro was admitted to the hospital on April 17, 1951. He was severely dyspneic and gravely ill. History, obtained from relatives and corroborated later by the patient, revealed that the patient had been engaged in his usual occupation of stoking furnaces until 3 p.m. At approximately 6:15 p.m. he experienced a choking sensation and became extremely dyspneic. A physician administered 1 mg. Adrenalin hydrochloride hypodermically, penicillin and Terramycin intramuscularly, and a 0.1 Gm. Nembutal suppository, between 7 and 7:45 a.m. All persons questioned stated that the symptoms continued to increase in severity in spite of the medication.

Past history revealed that the patient had experienced severe headaches and occasional mild dyspnea for more than a year. For six months, the patient had been under medical supervision for hypertension. During the three weeks prior to admission, he had been unable to lie flat in bed.

Physical examination revealed a semicomatose patient with blood pressure 240/140; pulse 136; respiration 60; and rectal temperature 99.2 F. Pink foam was noted at the corners of his mouth. Examination of the ocular fundi revealed mild narrowing and tortuosity of the arterioles. The neck veins were markedly distended. Cardiac dullness extended to the left anterior axillary line in the sixth intercostal space; the heart sounds could not be heard. Loud, moist, crepitant and subcrepitant rales, and rhonchi, were present over both lung fields. Expiration was prolonged. All deep reflexes were hypoactive.

Within a few minutes after arrival at the ward, alcohol-oxygen vapor was administered to the patient by nasal catheter according to method 3. After 15 minutes of therapy, the patient began to expectorate pink liquid material. At the end of 30 minutes, dyspnea had decreased remarkably and the patient was able to speak clearly. Improvement was progressive, subjectively and objectively, being marked at the end of one hour. Thirty minutes later, alcohol therapy was no longer considered necessary. Chest rales were still present but were decreased in number. Later, when the patient was resting, Mercuhydrin, 1 cc., and digitoxin, 1.2 mg. in divided doses, were given. No further digitalization was necessary.

On the following morning, the patient's blood pressure was 170/120; pulse, 102; respiration, 28; and rectal temperature, 101 F. A harsh, short, grade 3 systolic murmur over the aortic area and a loud reduplicated first heart sound at the apex were heard.

Laboratory findings were: urine, specific gravity 1.008 with 3 plus protein on admission and 1 plus protein at the time of discharge; maximum urine concentration of 1.010 and dilution of 1.008 during convalescence; nonprotein nitrogen 43; Kahn test negative. Chest films revealed cardiac enlargement and a "hypertensive contour." Circulation time (magnesium sulfate), during convalescence, was 25 seconds. Serial electrocardiograms, including standard and unipolar limb and chest leads, were recorded. The interpretation was: "abnormal tracing consistent with left ventricular hypertrophy and strain; vertical position with clockwise rotation."

On April 27, the patient was discharged free of symptoms to the Cardiac Clinic with the diagnosis of "hypertensive cardiovascular-renal disease."

In summary, this 58 year old Negro with hypertensive cardiovascular-renal disease developed acute paroxysmal pulmonary edema of the utmost severity. After approximately two and one-half to three hours of unabated progression, during which time no medication generally considered useful in this condition was given, alcohol-oxygen vapor was administered. Progressive and prompt recovery ensued.

Discussion

Selection of Cases. Evaluation of the usefulness of a new method of treatment in a paroxysmal, often fatal, syndrome is by no means easy. In order to insure the maximum objectivity of judgment, these patients have been observed by several members of the house staff in two different hospitals. In addition, most of the patients have been studied during and after the attack by one of us. The possibility of statistical comparison between two groups of patients, those tested with accepted procedures only, and those treated with these plus alcohol was considered at first; however, it did not seem practical because of the wide variety of causes, the extreme variability in the severity of the attacks, the differences in age and general health of the patients studied, and the fact that the judgment of various physicians was involved. Such variables would make the statistical validity of even a much larger group questionable. Therefore, the following plan was devised:

(a) The severity of the attacks was graded from 1 plus to 4 plus as follows: slight, 1 plus; moderate, 2 plus; severe, 3 plus; extremely severe, 4 plus. Only *severe* and *extremely severe*

cases of acute pulmonary edema (table 1*) were considered for alcohol treatment in order to exclude spontaneous recovery. In general, only the *acute cases* were accepted (table 1). However, early in the study, cases with a prolonged course were also accepted for treatment (table 2*) in order to evaluate the results in this type of pulmonary edema.

(b) The responsible physician was allowed to use any of the accepted procedures including drugs, venesection, oxygen, and positive pressure respiration. If, a suitable interval having elapsed, the attack continued unabated in spite of the above procedures, then alcohol inhalation was started. This plan was adopted in order to avoid the objection that life-saving procedures and drug therapy had been omitted to the possible detriment of the patients. Moreover, some patients came to the hospital after having received initial medication. On the other hand, and in spite of this program, in three attacks (nos. 12, 14, 17) no other accepted treatment for acute pulmonary edema was received before or during alcohol vapor therapy since response to this method was prompt and most satisfactory.

Evaluation of the Results. As already stated, only severe and very severe acute attacks were treated. In most of them, accepted procedures had been proved unsuccessful or no other treatment had been given. In some of them, death was considered imminent. Survival could not be taken as the only measure of success because in several clinical conditions the attack of pulmonary edema is merely one of the aspects of the syndrome and death may take place hours or days later because of the underlying basic disease (myocardial infarct, heart failure). For this reason, great attention was paid to objective and subjective evidence of improvement. Change from unconsciousness to consciousness; from labored respiration to even and slower breathing; from inability to speak to ability to even hold one's breath; from pale, taut face to a more normal aspect; slowing of the pulse; reduction of cyanosis; and auscultatory evidence of decrease in number and extension of pulmonary rales, were accepted as evidence of improvement. In particular, evidence that the sputum decreased in quantity, and that from a foamy, bubbling, abundant material it changed to small amounts of liquid or thick expectorate was taken as indication that the surface tension of the foam had been changed and that its content of air was diminished.

On the basis of the above data, it was considered that alcohol therapy was useful in 87 per cent of the attacks and dramatically so in 58 per cent of them.

This study suggests that the new method of treatment being discussed is worthy of use in cases of acute pulmonary edema of varied etiology whether or not other drugs or devices are also used.

Alcohol inhalation should be started at the earliest possible time and continued as long as required to produce a desirable effect. It should be tried again after initial sedation in the exceptional cases of poor toleration. When only the usefulness of therapy is involved, no waiting period should be allowed, and full use should be made of the combined effect of alcohol vapor and therapy of any other kind not specifically contraindicated.

In the acute, severe type of pulmonary edema, it is frequently impossible to ascertain the specific underlying disease responsible during the critical period. For this reason, a universally applicable treatment is particularly desirable.

Conclusions of Part II

Alcohol vapor has been administered to patients with acute pulmonary edema of severe or extremely severe type after failure of conventional medication. Improvement was prompt and marked in 58 per cent, definite though less prompt in another 29 per cent. Toleration of this therapy has been generally good. No specific contraindications to its use have been established.

Alcohol vapor was also administered to seven patients with subacute, prolonged pulmonary edema, all of whom were considered unlikely to survive. Clinical evidence of decrease of the foaming process was observed in three cases, even though the fatal course of the underlying

* See footnote, page 365.

condition (myocardial infarct, heart failure) caused death later on. Improvement was neither as prompt nor as marked as in the previous group.

Summary

Following experimental studies, clinical therapy of acute pulmonary edema utilizing the antifoaming effect of alcohol vapor by inhalation was studied.

Preliminary studies indicated that alcohol vapor by inhalation is well tolerated by normal subjects and cardiac patients. Four methods were tried. The two most practical are (a) one employing a nasal catheter, and (b) one making use of a positive pressure mask. The amount of alcohol detected in the blood was found to be small; its general effects, negligible.

Alcohol vapor was administered to 14 patients during 17 severe or extremely severe attacks of pulmonary edema. In general, alcohol was given after failure of routine medications; however, three cases received no conventional therapy prior to alcohol inhalation. In 58 per cent of the attacks, the result was favorable and there was good evidence of prompt relief. In 29 per cent of the attacks, the improvement was definite though less dramatic, so that improvement in a total of 87 per cent was noted. The clinical records of three selected cases are reported.

Alcohol vapor was also administered to seven patients with severe and prolonged pulmonary edema with poor to terminal status. In three, evidence of decrease of the foaming process was noted even though the fatal course of the underlying disease was not modified.

This preliminary study indicates that alcohol inhalation has a favorable action in clinical pulmonary edema, particularly of the acute paroxysmal variety. The desirability of a mode of therapy free of contraindications is noted and the possibility of using alcohol vapor in conjunction with conventional therapy is stressed.

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Addendum

Since completion of this report, 14 attacks of acute pulmonary edema in 12 patients have been treated with alcohol-oxygen vapor per nasal catheter according to the method described above. Several patients received no other treatment during the attack. The results of therapy parallel very closely those included in this report.

REFERENCES

[1] Luisada, A. A.: Beitrag zur Pathogenese und Therapie des Lungenödem. Arch. exper. Path. u. Pharmakol. **132:** 313, 1928.

[2] —: I fattori nervosi dell'edema polmonare acuto. In Frugoni: L'Edema polmonare acuto. Roma, Pozzi, 1931.

[3] —: On the treatment of paroxysmal pulmonary edema. Exper. Med. & Surg. **1:** 22, 1943.

[4] Sarnoff, S. J., and Farr, H. W.: Spinal anesthesia in therapy of pulmonary edema. Anesthesiology **5:** 69, 1944.

[5] Barach, A. L.: Edema of the lungs. Am. Pract. **3:** 27, 1948.

[6] Powers, S., Reed, C., and Gregarsen, M. I.: The effect of morphine on dogs in hemorrhagic and traumatic shock. Am. J. Physiol. **148:** 269, 1947.

[7] Scébat, L., Maurice, P., and Lenègre, J.: L'Action d'un diurétique mercuriel sur la pression sanguine des cavités droites du coeur chez les cardiaques. Arch. mal. coeur **42:** 1149, 1949.

[8] —, and Lenègre, J.: L'Action de la morphine sur la pression sanguine des cavités droites du coeur chez les cardiaques. Arch. mal. coeur **42:** 1157, 1949.

[9] Maloney, J. V., and Whittenberg, J. L.: Direct pulmonary effect of pressure breathing. Federation Proc. **10:** 88, 1951.

[10] Luisada, A. A.: Therapy of paroxysmal pulmonary edema by anti-foaming agents. Proc. Soc. Exper. Biol. & Med. **74:** 215, 1950.

[11] Luisada, A. A.: Therapy of paroxysmal pulmonary edema by antifoaming agents. Circulation **2:** 872, 1950.

[12] Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics. New York, Macmillan, 1941.

[13] Harger, R. N.: A simple micromethod for the determination of alcohol in biological material. J. Lab. & Clin. Med. **20:** 746, 1935.

Comparison of the Circulatory Effects of Epinephrine and Norepinephrine

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A comparison was made of the circulatory effects of *l*-epinephrine and *l*-norepinephrine when various doses were given either intravenously or intra-arterially into anesthetized animals. No significant difference was found between the effects of identical doses of the two drugs on the arterial blood pressure, heart rate and blood flow. The intensity and duration of effect of either drug varied roughly with the dose given.

THE LITERATURE on the circulatory effects of epinephrine and of norepinephrine reveals a variety of findings. In the presence of so many varied explanations concerning the circulatory effects of epinephrine and of norepinephrine, we decided to make a study of the influence of various concentrations of each of the two drugs on the heart rate and on the blood flow in the femoral arteries and veins and on the blood flow and blood pressure in the carotid artery of the anesthetized animal. In order to be able to separate as much as possible local effects from cardiac and systemic effects, the drugs were administered both intravenously and intra-arterially and the data on blood flow were correlated with those on the heart rate and arterial blood pressure.

Mertens and Kahlson,[1] Rein,[2] and Mertens and Rein[3] reported a decrease in the blood flow through the hind limb or resting muscle of anesthetized dogs upon intravenous administration of epinephrine, but Issekutz[4] obtained an increase. In anesthetized dogs, Rein and associates[5] observed a constrictor action of epinephrine and of "sympathetic impulses," if the muscle was at rest; but in the contracted or hyperemic muscle the injection of epinephrine or stimulation of the sympathetic nerves either was ineffective or brought about a dilator effect. Mertens and associates[6] and Rein and Schneider[7] demonstrated that epinephrine does not counteract the vasodilatation, and may even augment the already increased blood flow in active muscles.

In his plethysmographic studies on the skinned hind limbs of cats anesthetized with chloralose, McDowall[8] reported that the vessels of the muscles are tonically constricted by stimulation of fibers of the lumbar sympathetic nerves, in spite of the fact that they may be caused to dilate by injections of epinephrine or norepinephrine. By use of the venous occlusion plethysmograph, Allen and associates[9] obtained a fourfold to fivefold increase in blood flow in the human forearm during the first two minutes, when epinephrine was infused intravenously at the rate of 10 gammas per minute for 10 minutes. The changes in blood flow were much less conspicuous in the hand than in the forearm, indicating that the changes took place in the skeletal muscles. Konzett[10] found that in the dog isopropyl norepinephrine dilates the vessels of the limbs. Barcroft and Konzett[11] noted that infusions of norepinephrine at the rate of 3 gammas per minute caused a decrease in blood flow in the calf of the leg. Unlike epinephrine, norepinephrine has no transient vasodilator action in human skeletal muscle. In another communication,[12] they reported that norepinephrine infused intra-arterially caused vasoconstriction in the forearm and calf and reduced the blood flow, but intravenously there was no reduction in blood flow, while epinephrine caused a marked transitory vasodilatation, whether it was given intra-arterially or intravenously. They concluded that epinephrine caused transient vasodilatation in skeletal

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muscles while norepinephrine caused constriction of the vessels in skeletal muscle. Allen[13] noted that epinephrine in doses of 1 mg. given intramuscularly induced active dilatation of the blood vessels of skeletal muscle in the human forearm. Grant and Pearson[14] obtained an increase in limb volume and blood flow in the human forearm and leg. They reported that small doses of epinephrine regularly caused vasodilatation in human muscle. On the basis of intravenous administration of small doses in man, they concluded that epinephrine is a true vasodilator for muscle. However, Holling[15] found that when epinephrine was infused intravenously the vasodilatation was only transient and passed off in a few minutes, although the infusion continued. Graham[16] reported that in doses of 5 gammas per Kg. of body weight given intravenously, epinephrine produced a sharp vasoconstriction of the vessels of the cat's limb after slight passive dilatation.

By use of the cardiac catheterization technic in normotensive and hypertensive persons, Goldenberg and associates[17] found that epinephrine, by intravenous infusion in doses sufficient to cause significant hypertension, acted as an over-all vasodilator as well as a powerful cardiac stimulant. The primary action of norepinephrine was intense vasoconstriction. They noted that norepinephrine slows the human heart, diminishes the cardiac output and increases the peripheral resistance; its action in each case was opposite to that of epinephrine. Binet and Burstein[18] reported that the reflex vasodilator effect of epinephrine on the peripheral vessels is associated with inhibition of the tone of the vasoconstrictors and augmentation of that of the vasodilators. Ranges and Bradley[19] stated that the effect of epinephrine upon the vascular beds throughout the body varies from site to site; for instance, dilatation of the vessels of skeletal muscle and constriction of the arterioles of the skin and kidney.

In their plethysmographic studies of the effects of epinephrine on blood flow in the upper extremities of persons under basal conditions, Harpuder and associates[20] reported that injection of epinephrine in doses of 1 to 2 gammas into the brachial artery produced vasoconstriction. Intra-arterial doses of 0.5 to 0.1 gamma apparently are ineffective. Doses of 0.05 to 0.0002 gamma introduced intra-arterially caused vasodilatation, sometimes followed by vasoconstriction. In their studies on the hind legs of anesthetized cats, Griffith and associates[21–23] reported that the average effect of epinephrine injected intravenously at the rate of 0.004 mg. per Kg. of body weight per minute for five minutes was a 3 per cent increase in the blood flow, but either an increase or a decrease might occur. They stated that, as the rate of administration of epinephrine was increased, a balance between increasing degrees of local vasoconstriction and elevation of arterial pressure would explain the observed progressive decline in the augmentation of blood flow. When epinephrine was administered intra-arterially at the rate of 0.000,005 to 0.001 mg. per Kg. of body weight per minute for five minute periods, the changes in blood flow induced by the drug were explained on the basis of the prevailing evidence that minimally effective concentrations are vasodilating and higher concentrations, constricting. Only the highest rates of injection invariably produced constriction. Puccinelli[24] reported that upon injection of epinephrine into the femoral artery of the dog in minimal effective doses of 0.1 to 0.2 $\times$ 10^{-6} Gm., there was reduction in blood flow from the muscles; however, Clark[25] obtained dilatation followed by constriction of the vessels in the muscles of the cat when epinephrine was given intra-arterially in doses of about 0.05 $\times$ 10^{-6} Gm. He considered the capillaries as the site of such action of epinephrine. In their studies on skinned and intact hind limbs of cats under chloralose-urethane anesthesia, Folkow and associates[26] noted that in doses of 0.1, 1 and 2 gammas, epinephrine elicited a vasodilator response; higher doses, 3 and 5 gammas, caused predominantly vasoconstriction. Norepinephrine caused constriction of the blood vessels of both skin and muscle. They concluded that epinephrine in low concentrations dilates, whereas in high concentrations it constricts, the muscle vessels of the cat. In cats under chloralose anesthesia, Clark[27] recorded venous outflow from muscle, skin or intestine. In some cases the leg was skinned to prevent all chances of anastomosis

between skin and muscle. He obtained a two-fold response of muscle vessels to a single intra-arterial injection of minute amounts of epinephrine; first, dilatation and then constriction, although at times only constriction resulted. By the use of a modified Ludwig stromuhr, Roome[28] noted that the local effect of epinephrine upon the muscle blood vessels is, in all doses, dilatation of the capillaries and constriction of the arterioles, rather than a reversal of the capillary effect with increased concentrations.

By use of the Läwen-Trendelenburg perfusion method of assaying epinephrine, Trendelenburg[29] obtained evidence that this drug in all dilutions causes vasoconstriction in the legs of the frog. Upon administration of epinephrine intravenously, Woods and associates[30] obtained dilatation in the hind leg of the dog. They stated that epinephrine dilates muscle vessels. In their work on the perfused hind leg, Bülbring and Burn[31] reported that epinephrine causes vasodilatation in the muscles of the dog, but the dilator fibers were cholinergic. They noted[32] that in the dog's hind leg perfused with defibrinated blood, epinephrine caused vasoconstriction and this action was potentiated by prostigmine. From observations made by direct illumination of the sartorius muscle of the living cat, under the high-power objective of the microscope, Hartman and associates[33] reported that epinephrine intravenously administered produced precapillary constriction and dilatation of the muscle capillaries. Direct application of epinephrine, in concentrations that could not be tolerated systemically, produced constriction of the capillaries. Erlanger and Gasser[34] doubted the possibility of producing vasodilatation in skeletal muscles by epinephrine, and concluded that vasoconstriction of somatic and splanchnic areas is the main if not the only effect of continuous injection of epinephrine. They used extremely large doses, 6 to 11 cc. of a 1:1000 solution.

Gunning[35] reported diminished circulation and vasoconstriction in the vessels of skeletal muscles upon administration of large doses of epinephrine. The preliminary increase in outflow, he stated, is due to the forcing out of blood present in the vascular spaces into the veins by vasoconstriction. He suggested that fatigue of the vascular musculature led to a maintained secondary dilatation. Gruber[36] showed that, as in anesthetized animals, small doses of epinephrine injected intravenously into unanesthetized cats caused dilatation in the vessels of voluntary muscles as judged by increased venous outflow. He stated that vasodilatation is as much a characteristic action of epinephrine in weak solutions as vasoconstriction is in large doses. In their observations on the effects of epinephrine in the skinned limb, Hoskins and associates[37] reported that under all conditions of dosage, duration of administration, and resultant effects on blood pressure epinephrine caused expansion of the skinned leg. They found that the volume of the leg with intact skin contracted, but when the skin was removed it expanded, under the influence of epinephrine. They concluded that the contraction of the intact leg is due to vasoconstriction in the skin, while the expansion in the skinned leg indicates that epinephrine causes vasodilatation in the muscle. Duncanson and associates[38] injected norepinephrine intravenously at a rate of 2, 5, and 10 gammas per minute for five minutes in each instance. There was no change in blood flow of the forearm when a rate of 2 gammas per minute was used, but when the rate was 5 and 10 gammas per minute there was a slight reduction in flow when both systolic and diastolic pressures were raised.

Methods

Dogs weighing between 15 and 25 Kg. were used in this study. In order to determine if there is species difference in the reaction to epinephrine and norepinephrine, a number of observations were made on one monkey and one cat. Most of the animals were anesthetized with pentobarbital sodium given intravenously (25 mg. per Kg. of body weight), but a few were anesthetized with ether given by inhalation. To maintain an even level of anesthesia when pentobarbital sodium was used, a certain quantity of the drug was dissolved in the solution of heparin and was administered along with the heparin drip throughout the experiment. The blood pressure was recorded from the carotid artery by means of a mercury manometer writing on a kymograph. The heart rate was recorded electrocardiographically, and the blood flow by use of our modification of the Dumke and Schmidt[39] bubble flowmeter. Both fem-

oral arteries were isolated; after heparinization of the animal, a bubble flowmeter was connected to each femoral artery. In some cases a bubble flowmeter also was connected to the femoral vein and another one to the carotid artery.

Heparinization was achieved in the following manner. Initially, 2 or 3 cc. of heparin sodium containing 1000 units per cc. was injected intravenously, and this was followed by the intravenous drip administration of 1 per cent heparin in saline solution throughout the experiment. With continuous heparinization and a maintained steady level of anesthesia, the blood flow and the blood pressure were maintained in a steady status and returned to control levels after every procedure throughout the period of study, which lasted as long as seven hours. The flowmeters were calibrated before they were connected to the blood vessels, and the volumes of flow were determined by the time required for a bubble of air to travel between two fixed points on the meter.

In some experiments, the effect of electric stimulation of the muscles of the extremity was investigated. For that purpose, special units containing the electrodes for stimulation were placed at the base of the thigh on both the femoral and the sciatic nerves of each leg.

The effects of varying doses of *l*-epinephrine bitartrate and of *l*-norepinephrine bitartrate on the peripheral circulation were studied after control blood flow, heart rate and blood pressure were established before each intra-arterial or intravenous injection. The dose varied from 0.01 to 10 gammas per Kg. of body weight.

To separate (1) the reaction to epinephrine and to norepinephrine of the blood vessels of the skin from (2) the reaction of the vessels of the muscles and to be able to determine to what extent the skin took part in the effect of these drugs, in a large number of experiments one limb was kept intact while the contralateral limb was skinned. The extremity was skinned by making a circular incision through the skin at the junction of the thigh with the trunk. The skin was carefully separated from the subcutaneous tissues of the whole extremity down to the insertion of the Achilles tendon. After the bleeding vessels had been carefully ligated, the skin was pulled back to its original position over the extremity. The distal edges of the skin were sutured in place to proximal edges along the circular incision. This procedure provided natural protection for the muscles and yet completely separated the skin from the rest of the tissues of the limb. In a number of instances a tourniquet was applied over the distal end of the tibia at the point where the skin was separated from underlying tissues. To eliminate the influence of vagal reflex effects on the heart rate and blood pressure, a number of experiments were performed in which epinephrine and norepinephrine were administered before and after bilateral cervical vagotomy.

Results

The intravenous administration of epinephrine or norepinephrine produced an immediate increase in blood flow concomitant with the increase in blood pressure. After this increase, the flow gradually returned, within four minutes, to the rate that had obtained before injection. Detailed data on the blood pressure or blood flow or both are presented in figures 1, 2, and 3. When either epinephrine or norepinephrine was injected intravenously in equivalent doses, the changes in blood pressure and in blood flow were practically indistinguishable. The repeatedly observed findings support the statement that intravenously administered epinephrine or norepinephrine in the dog produces a similar transient marked increase in blood flow accompanying the increase in blood pressure. Within four minutes, the values for blood flow returned to control levels. Sometimes, after the marked transient increase, there was a slight reduction in blood flow. The magnitude of these changes varied roughly according to dose, but the effects of epinephrine and of norepinephrine on the blood flow and blood pressure were so much alike that, for all practical purposes, they can be considered identical for exactly equal doses. The influence on the blood flow in the skinned limb of the dog was the same as that on the blood flow of the limb with intact skin. The contour of the blood flow curves for the skinned limb was similar to that of the curves for the intact limb, even though control values were not identical.

Accompanying the rise in blood pressure and the increase in blood flow was a reduction in heart rate after intravenous administration of either epinephrine or norepinephrine. The effects on the heart rate are presented graphically in figures 4 and 5. Immediately after intravenous injection in the intact animal, the arterial blood pressure increased (fig. 2) and was followed by reflex bradycardia (figs. 4 and 5). The magnitude of the increase in blood pressure was roughly proportional to the intravenous dose, no matter whether epinephrine or norepinephrine was injected. Occa-

sionally, there was a slight initial increase in heart rate before the reflex bradycardia occurred, concomitant with the increase in arterial blood pressure. This initial transient tachycardia occurred more frequently when epinephrine was used than when norepinephrine was used. These findings support the concept that the marked increase in arterial blood pressure upon the intravenous injection of epinephrine or norepinephrine, in the presence of intact vagus

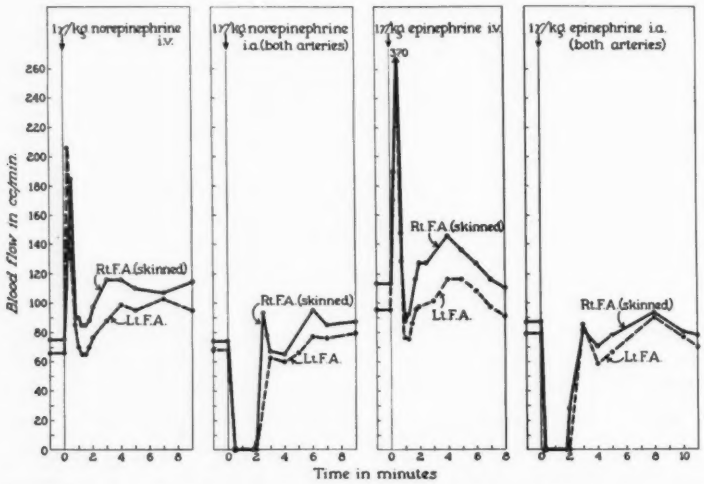

FIG. 1. Blood flow curves for the right and left femoral arteries before and after intravenous and intra-arterial injection of 1 gamma of *l*-norepinephrine and of 1 gamma of *l*-epinephrine per Kg. of body weight. One may note the immediate transient but marked increase in blood flow after the intravenous and the immediate marked decrease after intra-arterial injection of either epinephrine or norepinephrine in both the skinned and the intact limb.

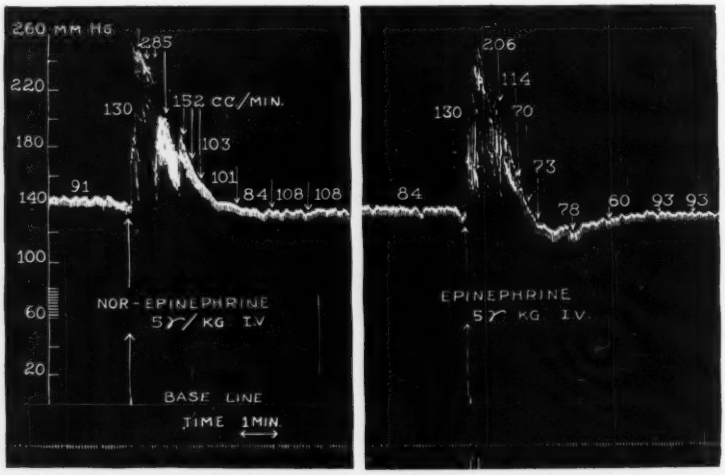

FIG. 2. The blood flow values, for the right femoral artery before and after intravenous injection of 5 gamma of *l*-norepineprhine or 5 gamma of *l*-epinephrine per Kg. of body weight, are plotted in cubic centimeters per minute on the simultaneous blood pressure record obtained by a mercury manometer connected to the carotid artery. One may note the similarity in effect of the two drugs on the blood flow and on the blood pressure.

nerves, reflexly brings about a slowing of the heart through the nervous mechanisms of the carotid sinus and aortic arch. In the absence of this reflex, consequent to severance of the vagus nerves, even though the increase in blood pressure is greater upon the intravenous injection of epinephrine or of norepinephrine, the direct action of either of these drugs on the heart is stimulatory.

After both vagus nerves were cut in the neck, the reflex bradycardia, after injection of either epinephrine or norepinephrine in doses of 2 or 5 gammas per Kg. of body weight, was replaced by tachycardia (figs. 4 and 5) even though the increase in blood pressure not only persisted but became slightly greater in magnitude than before vagotomy. However, 1 gamma of either drug per Kg. of body weight often produced slight bradycardia, even after vagotomy, in the anesthetized animal. This confirms the report of Tuohy and one of us (Essex)[40] who found that even after vagotomy the heart showed evidence of vagus-like slowing when epinephrine was given intravenously. Occasionally in this group the injection of norepinephrine before and also after vagotomy produced a slightly greater pressor effect than did epinephrine. On the average, there was more often slightly greater tachycardia when norepinephrine was used after vagotomy and sometimes slightly greater bradycardia before vagotomy.

In a group of trained dogs the heart rate was recorded electrocardiographically immediately before and for 90 seconds after the intravenous injection of equivalent doses of epinephrine or norepinephrine (1 gamma per Kg. of body weight). In five of the 10 dogs the initial injection was epinephrine; to the other five, norepinephrine was given first. Both epinephrine and norepinephrine produced marked bradycardia in the trained animal. Figure 5 shows the control heart rates and the changes in heart rate produced 15, 30, 45, 60, 75 and 90 seconds respectively after injection of each drug. Bradycardia of varying magnitude under the influence of either drug is demonstrated. On the average norepinephrine produced a slightly greater degree of bradycardia than epinephrine, but both slowed the heart. These data demonstrate that both drugs produced bradycardia reflexly when given intravenously in the presence of intact vagus nerves. The bradycardia in the trained animal was much greater than when the animal was anesthetized. This is probably due to the depressive effect that barbiturate anesthesia has on the reflex mechanisms involved.

The intra-arterial administration of either epinephrine or norepinephrine (fig. 1) brought about either reduction or complete cessation of blood flow in the artery used for the injection, depending upon the magnitude of the dose. Very small doses usually produced transient slight reduction, but larger doses (fig. 1) produced complete cessation of blood flow in the artery for several minutes. Whenever the

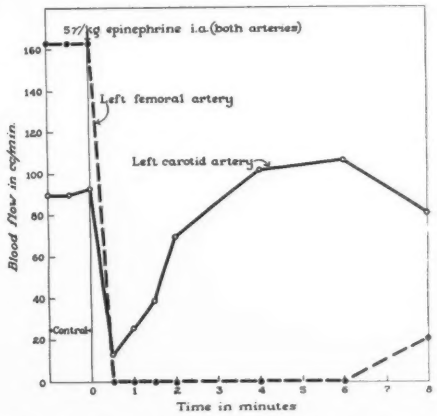

FIG. 3. Graph showing that simultaneous injection of 5 gamma of epinephrine per Kg. of body weight into both carotid and femoral arteries produced complete cessation of flow in the femoral artery for six minutes but only a reduction of flow in the carotid artery.

intra-arterial injection of either of the two drugs caused reduction but not complete cessation of blood flow in the injected artery, this was followed immediately by an increase in flow and in blood pressure as a result of the cardiac effect of the drug when it was carried back to the heart by the venous blood returning from the extremity used for the injection. Often, upon recovery of the circulation in the area supplied by the artery following the prolonged cessation of blood flow in that artery, there was a transient increase in the blood flow before the gradual return to preinjection levels. This

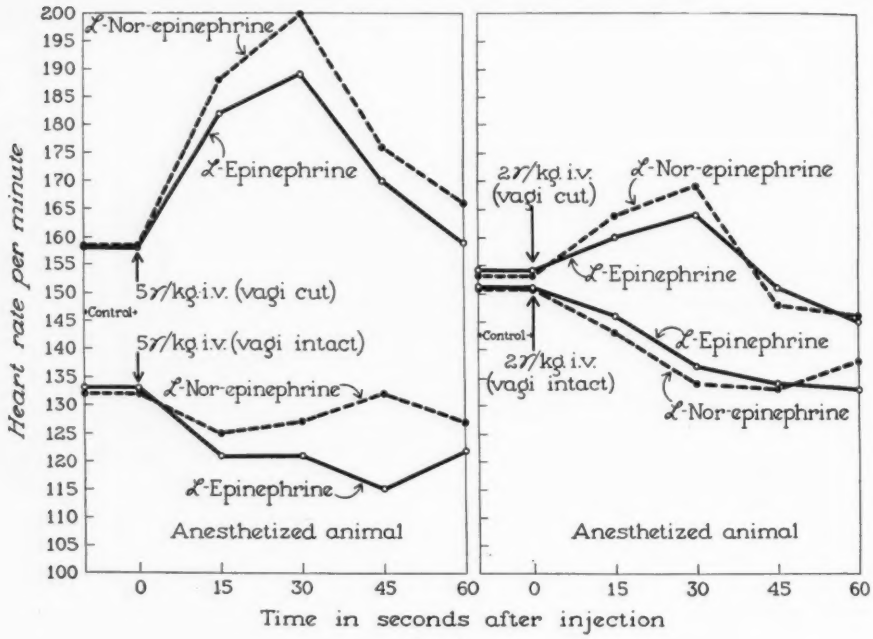

FIG. 4

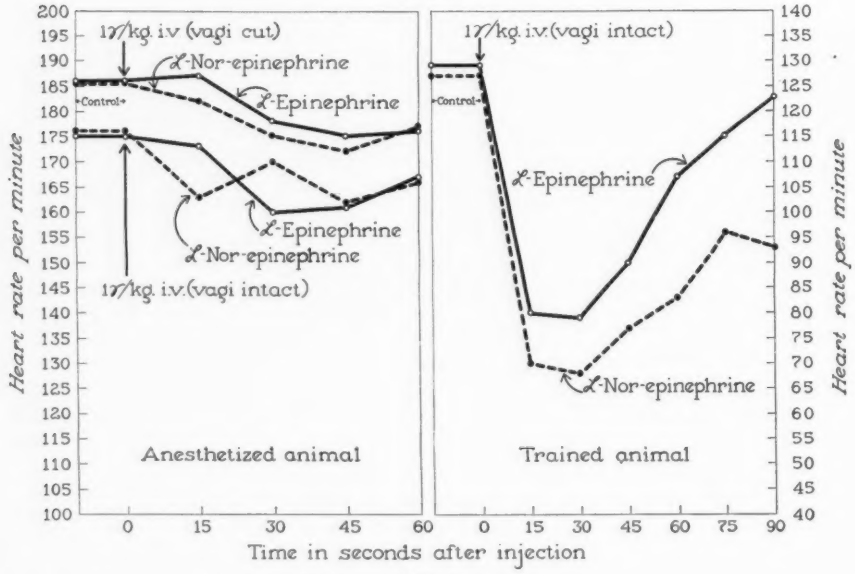

FIG. 5

FIGS. 4 and 5. The influence of intravenous epinephrine and norepinephrine on the heart rate before and after vagotomy. One may note the more marked bradycardia in the trained intact animal.

might be attributable to the metabolites which accumulated in the area during complete cessation of blood flow and which were washed out upon recovery of the ramifications of that artery from the vasoconstrictor effect of the drugs. This was confirmed by the increase in

blood flow which occurred upon release of the clamp from the artery which was mechanically occluded for a period equal in duration to that of cessation of flow induced by intra-arterial injection of either epinephrine or norepinephrine. From the data obtained on blood flow and their correlation with blood pressure, we find no indication of a vasodilator effect of either drug by any of the doses administered in this study.

The control blood flow in the electrically stimulated extremity was greater than that of the contralateral unstimulated limb. The administration of epinephrine or norepinephrine

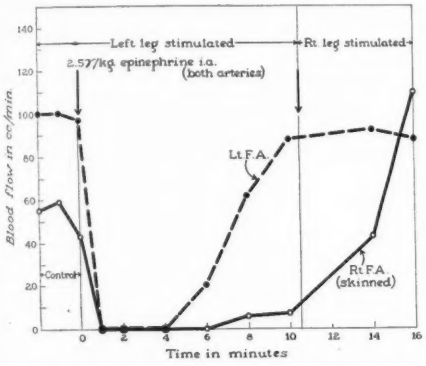

FIG. 6. Blood flow curves for the right and left femoral arteries before and after intra-arterial injection of epinephrine during electric stimulation of one extremity. One may note the greater flow in the stimulated extremity and the shorter duration of the epinephrine effect.

intra-arterially caused reduction or complete cessation of the blood flow but the duration of the cessation of flow was much shorter during stimulation of the extremity (fig. 6). Furthermore, recovery from vasoconstriction caused by epinephrine was hastened upon stimulation of the limb (fig. 6).

The findings obtained from the intravenous and intra-arterial injection of epinephrine or norepinephrine to one cat and one monkey were very similar to those herein reported on dogs.

In some experiments a bubble flowmeter was connected to the corresponding femoral vein in addition to the one on the femoral artery. Even during complete cessation of blood flow in the artery as a result of administration of epinephrine or norepinephrine intra-arterially, the flow in the vein was much reduced but was not completely arrested. This was attributed to the tributaries supplying blood to the vein outside the area of distribution of the artery under observation. This idea was substantiated by the fact that complete occlusion of the artery by a clamp did not produce complete cessation of blood flow in the vein but occlusion of the tributaries to the vein led to complete cessation of flow in the femoral vein.

A number of experiments were performed in which the blood flow was measured in the carotid artery. The administration into the carotid artery of the same dose of either epinephrine or norepinephrine which produced complete cessation of flow in the femoral artery would only produce moderate reduction in carotid blood flow when injected into the carotid artery (fig. 3). The mechanism of this phenomenon is under investigation.

A phenomenon which was repeatedly observed deserves comment. In most experiments, no matter whether the very first injection was epinephrine or norepinephrine its effect on the heart rate, blood pressure and blood flow was often slightly greater than the second and other consecutive injections even though the doses were identical. For instance, if epinephrine was given first, and, after its apparent effect had disappeared, an injection of norepinephrine in identical dose was given, the effect of epinephrine would be slightly greater even though the dose was identical to the norepinephrine which followed it. When this order was reversed, namely, if the first injection was norepinephrine, its effect would be slightly greater. One wonders whether this could be in part the basis for the reports that norepinephrine is slightly less effective than epinephrine in certain aspects, and epinephrine in other aspects. This observation suggested the advisability of alternating the injections of the various doses of either drug. One day the initial injection was made with epinephrine and on the second day the order was reversed starting with norepinephrine.

SUMMARY

The circulatory effects of *l*-epinephrine bitartrate and of *l*-norepinephrine bitartrate were

studied in the heparinized dog under pentobarbital sodium or ether anesthesia. The former drugs were administered either intravenously or intra-arterially. The dose varied from 0.01 to 10 gammas per Kg. of body weight. The heart rate was recorded electrocardiographically; the blood pressure, by use of a mercury manometer connected to the carotid artery. The blood flow in the two femoral arteries and in addition sometimes in one femoral vein and one carotid artery was measured by use of bubble flowmeters. The simultaneous changes in blood pressure and blood flow produced by *l*-epinephrine were practically indistinguishable from those produced by *l*-norepinephrine. Administered intravenously, either of the drugs in equivalent doses produced an immediate increase in blood pressure of practically the same magnitude, and the occasionally resulting tachycardia was consistently followed by reflex bradycardia in the presence of intact vagus nerves during the peak of increased blood pressure. After bilateral cervical vagotomy there was a direct stimulatory effect on the heart of effective doses of either drug which resulted in an increase in heart rate. Immediately before the maximal increase in arterial blood pressure following the intravenous injection of either *l*-epinephrine or *l*-norepinephrine, there was a transient increase of several hundred per cent in blood flow accompanying the augmentation in the force of cardiac action and in cardiac output. This was attributed to the direct cardiac stimulatory effect of the drugs. Often, a moderate or very slight reduction in blood flow occurred before the return to the preinjection level within about four minutes. Intra-arterial injection of *l*-epinephrine or *l*-norepinephrine brought about an immediate vasoconstriction in the supplied area with reduction or cessation of blood flow in the skinned, as well as in the intact, limb. The degree and duration of the reduction or cessation of blood flow depended upon the dose. Very small intra-arterial doses caused slight and transient reduction in blood flow without significant effect on heart rate or arterial blood pressure. Larger doses caused a great reduction or complete cessation in blood flow in the arteries used for the injection. This was independent of the effects on the heart rate or arterial blood pressure.

REFERENCES

[1] MERTENS, O., AND KAHLSON, G.: Das Herzminutenvolumen des Ganztieres unter Einwirkung von Adrenalin. Ber. ü. d. ges. Physiol. u. Pharmakol. **96:** 674, 1936–1937.

[2] REIN, H.: Über die physiologischen Aufgaben des Adrenalins als Kreislaufhormon. Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch. p. 27, 1937.

[3] MERTENS, O., AND REIN, H.: Die Beeinflussung des respiratorischen Stoffwechsels durch das autonome Nervensystem. Arch. f. d. ges. Physiol. **241:** 402, 1938.

[4] ISSEKUTZ, B. V., JR.: Die Wirkung von Gefässmitteln auf den lokalen Stoffwechsel des Muskels. Arch. f. exper. Path. u. Pharmakol. **197:** 313, 1941.

[5] REIN, H., HOLZER, W., AND OTTO, U.: Über die Abhängigkeit der zentralnervösen Durchblutungssteuerung vom Grundzustand der Gewebe. Arch. f. d. ges. Physiol. **243:** 468, 1940.

[6] MERTENS, O., REIN, H. AND VALDECASES, F. G.: Gefässwirkungen des Adrenalins im ruhenden und arbeitenden Muskel. Arch. f. d. ges. Physiol. **237:** 454, 1936.

[7] REIN, H., AND SCHNEIDER, M.: Die Interferezen verscheidener Regulationen im Muskelgefässnetz. Ztschr. f. Biol. **91:** 13, 1930.

[8] MCDOWALL, R. J. S.: The responses of the blood vessels of the muscles with special reference to their central control. J. Physiol. **111:** 1, 1950.

[9] ALLEN, W. J., BARCROFT, H. AND EDHOLM, O. G.: On the action of adrenaline on the blood vessels in human skeletal muscle. J. Physiol. **105:** 255, 1946.

[10] KONZETT, H.: Neue broncholytisch hochwirksame Körper der Adrenalinreche. Arch. f. exper. Path. u. Pharmakol. **197:** 27, 1940.

[11] BARCROFT, H., AND KONZETT, H.: A comparison of the actions of noradrenaline and adrenaline on the blood vessels of human skeletal muscle. J. Physiol. **110:** 11*P*, 1949.

[12] —, AND —.: On the actions of noradrenaline, adrenaline and isopropyl noradrenaline on the arterial blood pressure, heart rate and muscle blood flow in man. J. Physiol. **110:** 194, 1949.

[13] ALLEN, W. J.: Action of adrenaline, ephedrine, and methedrine on circulation in man. Clin. Sc. **6:** 269, 1948.

[14] GRANT, R. T., AND PEARSON, R. S. B.: The blood circulation in the human limb; observations on the differences between the proximal and distal parts and remarks on the regulation of body temperature. Clin. Sc. **3:** 119, 1938.

[15] HOLLING, H. E.: Observations on oxygen content

of venous blood from arm vein and on oxygen consumption of resting human muscle. Clin. Sc. **4:** 103, 1939.

[16] GRAHAM, J. D. P.: The cardiovascular actions of some amines related to adrenaline. Quart. J. Pharm. & Pharmacol. **17:** 19, 1944.

[17] GOLDENBERG, M., PINES, K. L., BALDWIN, E. DEF., GREENE, D. G., AND ROH, C. E.: The hemodynamic response of man to nor-epinephrine and epinephrine and its relation to the problem of hypertension. Am. J. Med. **5:** 792, 1948.

[18] BINET, LÉON AND BURSTEIN, M.: Sur la vasodilatation périphérique d'origine adrénalinique. Compt. rend. Soc. de biol. **141:** 630, 1947.

[19] RANGES, H. A., AND BRADLEY, S. E.: Systemic and renal circulatory changes following the administration of adrenin, ephedrine, and paredrinol to normal man. J. Clin. Investigation **22:** 687, 1943.

[20] HARPUDER, K., BYER, J. AND STEIN, I. D.: The effect of intra-arterial injection of adrenalin upon blood flow of the human forearm. Am. J. Physiol. **150:** 181, 1947.

[21] GRIFFITH, F. R., JR., OMACHI, A., LOCKWOOD, J. E., AND LOOMIS, T. A.: The effect of intravenous adrenalin on blood flow, sugar retention, lactate output and respiratory metabolism of peripheral (leg) tissues in the anesthetized cat. Am. J. Physiol. **149:** 64, 1947.

[22] GRIFFITH, F. R., JR., COLE, D. C., AND THOMAS, D. B.: Comparative effect of intravenous glucose and adrenalin on blood flow, oxygen utilization and glucose retention by hind leg tissues of anesthetized cats. Am. J. Physiol. **157:** 205, 1949.

[23] GRIFFITH, F. R., JR., LOCKWOOD, J. E., AND LOOMIS, T. A.: Effect of intra-arterially injected adrenalin on blood flow, sugar retention and lactate output of leg tissues of anesthetized cats. Am. J. Physiol. **146:** 677, 1946.

[24] PUCCINELLI, E.: Sopra alcune modificazioni del delflusso venoso femorale per iniezione di adrenaline. Considerazioni sulla partecipazione de circolo femorale ad alcuni fenomeni vasomotori. Riv. di pat. sper. **12:** 261, 1934.

[25] CLARK, G. A.: Adrenaline vaso-dilatation in voluntary muscle. J. Physiol. **84:** 344, 1935.

[26] FOLKOW, B., FROST, J., AND UVNÄS, B.: Action of adrenaline, nor-adrenaline and some other sympathomimetic drugs on the muscular, cutaneous and splanchnic vessels of the cat. Acta physiol. Scandinav. **15:** 412, 1948.

[27] CLARK, G. A.: The vaso-dilator of adrenaline. J. Physiol. **80:** 429, 1934.

[28] ROOME, N. W.: The effects of intra-arterial epinephrin on the blood flow in an extremity. Am. J. Physiol. **123:** 543, 1938.

[29] TRENDELENBURG, PAUL: Über die Adrenalinkonzentration im Säugetierblut. Arch. f. exper. Path. u. Pharmakol. **79:** 154, 1915.

[30] WOODS, G. G., NELSON, V. E., AND NELSON, E. E.: The effect of small amounts of ergotamine on the circulatory response to epinephrine. J. Pharmacol. & Exper. Therap. **45:** 403, 1932.

[31] BÜLBRING, E., AND BURN, J. H.: The sympathetic dilator fibres in the muscles of the cat and dog. J. Physiol. **83:** 483, 1934.

[32] BÜLBRING, E., AND BURN, J. H.: The interrelation of prostigmine, adrenaline and ephedrine in skeletal muscle. J. Physiol. **101:** 224, 1942.

[33] HARTMAN, F. A., EVANS, J. I., AND WALKER, H. G.: Control of capillaries of skeletal muscle. Am. J. Physiol. **90:** 668, 1929.

[34] ERLANGER, J. AND GASSER, H. S.: Studies in secondary traumatic shock. III. Circulatory failure due to adrenalin. Am. J. Physiol. **49:** 345, 1919.

[35] GUNNING, R. E. L.: The effects of adrenin on the distribution of the blood. IV. Effect of massive doses on the outflow from muscle. Am. J. Physiol. **43:** 395, 1917.

[36] GRUBER, C. M.: The arterial blood pressure and the blood flow in skeletal muscles in unanesthetized cats as influenced by the intravenous injection of epinephrin. Am. J. Physiol. **89:** 650, 1929.

[37] HOSKINS, R. G., GUNNING, R. E. L., AND BERRY, E. L.: The effects of adrenin on the distribution of the blood. I. Volume changes and venous discharge in the limb. Am. J. Physiol. **41:** 513, 1916.

[38] DUNCANSON, D., STEWART, T., AND EDHOLM, O. G.: Effect of l-arterenol on the peripheral circulation in man. Federation Proc. **8:** 37, 1949.

[39] DUMKE, P. R., AND SCHMIDT, C. F.: Quantitative measurements of cerebral blood flow in the Macacque monkey. Am. J. Physiol. **138:** 421, 1943.

[40] TUOHY, E. B., AND ESSEX, H. E.: A comparative study of the physiologic activity of cobefrin and epinephrine. Surgery **1:** 564, 1937.

Pressor Substances in Arterial Hypertension

IV. Quantitative and Qualitative Studies of Pherentasin

By Dean F. Davies, Ph.D., M.D., Norman S. Olsen, Ph.D., and Henry A. Schroeder, M.D.

Pherentasin is the only pressor substance found in blood of hypertensive patients which is not found in normal blood. This study defines its unit and compares its concentration with diastolic blood pressure level, type of hypertension, and age of patients. Lack of correlation between blood pressure level and pherentasin content suggests considerable variation in the amount of depressor substances in these patients. Chemical studies of pherentasin and its partial, tentative formula are discussed. Demonstration of the existence of an additional pressor fraction from blood which is volatile in alkaline solution is described.

PHERENTASIN, a pressor substance present in the arterial blood of hypertensive, but not of normotensive, patients, was demonstrated by Stock and Schroeder,[1] and confirmed by Olsen and Schroeder.[2] Its occurrence in different types of hypertension was reported by Schroeder and Olsen.[3] The present report concerns quantitative studies and chemical properties of the substance discovered during further purification of the concentrated extracts used for assay in the previous investigation,[2] and the data on 50 cases subsequently studied.

Quantitation by Assay

Definition of a Unit of Pherentasin

We suspected that the criteria initially used for the rat pressor assay to establish the existence of pherentasin were unnecessarily rigid.[3] Analysis of the data demonstrated this to be true. Furthermore, attempts to isolate and identify the material, which were limited by a purely qualitative test for its presence or absence, would be expedited by an estimate of the amount in each fraction. In addition, the preliminary finding that pherentasin is more frequently found in the renal than in the neurogenic or endocrine types of hypertension raises the question of the relative concentrations which will be observed.

Therefore, a statistical analysis of the responses of the diastolic blood pressure of hypertensive rats to the injection of extracts of normotensive human arterial blood has been made. The first step involved a demonstration of the lack of delayed pressor effect from depressor substances (of the adenine series[2]) present in the extracts. Obviously a pressor reaction caused by anoxia consequent to hypotension would invalidate the method as a means of assay of pressor substances. As shown in figure 1, immediate depressor responses were not correlated with the delayed pressor effect of pherentasin. By definition[3] the extract has not been considered positive unless diastolic pressure was elevated at least 12 mm. Hg 10, 15, or 20 minutes after injection. Measurements at these intervals were used in the analysis.

Close examination of the effects on blood pressure of the injection of normotensive and hypertensive extracts into rats showed that false positive responses did not occur, while false negative responses in single tests were not uncommon. Whether or not failure to respond to the pressor substance was due to too deep anesthesia, a refractory stage of hypertension of individual rats, or greater sensitivity of a particular rat to counteracting depressor contaminants in the extract is not known. How-

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ever, the degree of depression of blood pressure in the false negative assays was not significant, and they were considered as assays with zero rather than a negative pressor response in the analysis.

The unit is defined as the amount of pherentasin present in an extract of 20 ml. of blood which will, in at least three assays on three renal hypertensive rats, produce an average maximum elevation of diastolic blood pressure at 10, 15 or 20 minutes after injection exceeding

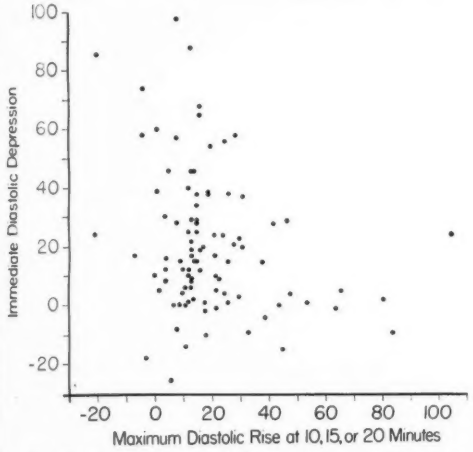


FIG. 1. Lack of correlation between immediate depressor responses and delayed pressor responses of pherentasin extracts injected into hypertensive rats. The absence of a correlation makes it highly improbable that the initial hypotension induced by the injection is related to the pressor response in an etiologic sense. This point is critical to the interpretation of the results.

the 2 per cent level of probability for normotensive extracts. At present this requires a mean rise of 7 mm. Hg, a value which may change with improvement in technics of purification. According to these criteria 40 per cent of 18 extracts of hypertensive blood which had been called "inactive" by previous criteria were found to contain pressor material. Of an additional six samples called "doubtful" because of not meeting the previous criteria, four were found to be pressor with 1.1, 1.2, 1.7 and 2.1 units, and two gave high normal values with 0.93 and 0.96 units.

Blood Pressure Elevation and Blood Pherentasin

Figure 2 shows that there was no correlation between diastolic blood pressure of hypertensive patients and the amount of pherentasin found in their blood. While elevation of diastolic blood pressure was limited to a two-fold increase over normal values, the observed concentration of pherentasin ranged from less than 1 to 7 units. The occurrence of pherentasin in the blood of patients with cardiac failure,

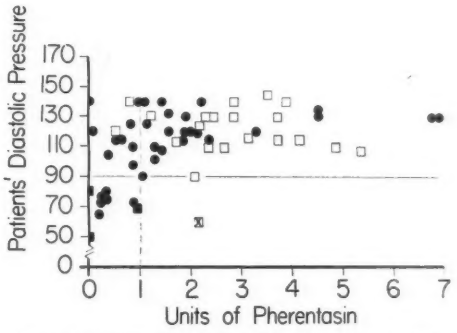


FIG. 2. Units of pherentasin in blood plotted against diastolic level of blood pressure in normotensive and hypertensive subjects.

Unpublished series, closed circle; cases recalculated from original data of published results, open square; rheumatic heart disease with mitral stenosis and cardiac decompensation, crossed square; best estimate of concentration from available data, closed square. The vertical dotted line is placed at 1.0 unit, the solid horizontal one at 90 mm. Hg. There is no correlation between the amount of pherentasin in blood and the diastolic pressure. Note that the blood of only 10 of 50 hypertensive subjects contained less than 1.0 unit as measured by the rat pressor test.

shock and other circulatory diseases has not been adequately studied, but that of one woman with mitral stenosis, tricuspid insufficiency and a blood pressure of 110/60 contained significant levels. In the extracts of other normotensive subjects there was significantly less or no pherentasin.

Blood Pherentasin and Nature of Hypertension

It has already been shown[3] that blood pherentasin is found more frequently in the renal type

TABLE 1.—*Pherentasin Concentration in Blood According to Type and Known Duration of Hypertension*

Patient No.	Sample No.	Age & Sex	Blood Pressure	Known Duration of Hypertension Yrs.	Units of Pherentasin	Diagnosis & Remarks
			Renal Type n = 12			
1	141	50M	215/115	14	3.71	
	199	51M	230/110	15	0.86	
Mean		50.5	223/113	14.5	2.29	
2	179	42M	185/125	14	1.14	
3	211	62F	210/120	14	0.07	
4	158	52F	260/140	11	1.10	
5	174	60F	240/130	7	1.89	
6	150	52M	226/130	5	2.86	
7	209	50F	225/115	4	0.64	
8	206	65F	254/130	3½	6.93	Diabetes mellitus. Poor response to TEAC
9	147	42F	220/110	1	2.68	
10	184	38F	194/130	1	6.79	
11	185	56M	250/140	½	2.22	
12	189	36M	185/98	⅙	0.86	Diabetes mellitus
Mean		50.5	223/123	6.3	2.46	
			Neurogenic Type n = 8			
13	133	46F	210/110	14	2.36	
	203	47	230/120	15	3.28	
Mean		46.5	220/115	14.5	2.82	
14	134	49M	170/108	4	5.35	Asthma
	163	50		5	1.43	
Mean		49.5		4.5	3.39	
15	135	56F	230/116	3	3.14	
16	159	53M	250/140	3	2.86	Duodenal Ulcer
17	156	52M	246/130	2	3.71	
18	173	55M	190/115	2	0.57	
19	200	47F	220/140	2	0.0	
20	182	39M	185/105	1	0.36	
Mean		49.8	214/121	4.0	2.11	
			Endocrine Type n = 9			
21	143	47F	220/140	20	0.82	Hyperadrenocorticalism
22	149	43F	240/145	9	3.50	Hyperthyroidism; cardiac decompensation. Amenorrhea 4 years at age 35
23	168	47F	220/130	6	4.52	Endocrine hypertensive syndrome
24	192	35F	225/132	5	1.57	Endocrine hypertensive syndrome
25	142	39F	184/120	4	0.52	Endocrine hypertensive syndrome
26	188	46F	218/125	3	0.82	Endocrine hypertensive syndrome
	208	47	205/115	4	2.36	
Mean		46.5	211/120	3.5	1.59	
27	178	44F	162/102	2	1.28	Endocrine hypertensive syndrome
28	181	48F	195/120	2	1.90	Artificial menopause from gynecologic operation
29	162	39F	180/120	1	1.57	Hypo-ovarianism. Coarctation of aorta
Mean		43.2	204/125	5.4	1.92	

Figures underlined were not used in calculating mean values.

TABLE 1.—*Continued*

Patient No.	Sample No.	Age & Sex	Blood Pressure	Known Duration of Hypertension Yrs.	Units of Pherentasin	Diagnosis & Remarks
			Miscellaneous n = 15			
30	144	41F	230/115	21	2.90	Neurogenic. Cerebrovasc. accident
31	151	52F	240/140	15	3.90	Neurogenic. Cerebrovascular accident. Early cardiac decompens.
32	197	57M	215/110	15	1.28*	? Renal. Cerebrovascular accident
33	153	57M	170/90	12	2.07	Renal type. Cerebrovas. accident
34	164	51M	234/114	12	1.86	Nephritis. Rheumatic fever. Lead poisoning
35	186	57M	140/120	9	2.00	Agnogenic. Cardiac decompensation
36	210	47F	260/134	7	0.0*	Pre-eclampsia. Pyelonephritis. ? Endocrine
37	166	37M	200/140	7	1.00	Agnogenic. Laennec's cirrhosis
38	132	23M	220/114	6	1.70	Coarctation of aorta, adult type
39	148	48M	220/130	5	2.40	Malignant. Cardiac decompensation
40	167	45M	200/140	4	1.43	Renal. Cardiac decompensation
41	157	54F	220/130	2	2.38	RHD. Aortic stenosis and insufficiency
42	160	41M	208/124	1	2.18	Renal. Malignant
43	183	57M	210/135	1	4.53	Neurogenic. Cardiac decompensation
44	169	63M	190/120	½	2.14	Neurogenic. Cerebrovasc. accident
Mean		48.7	210/124	7.8	2.12	
			Normotensives n = 19			
45	180	33M	120/70		0.29	Normal
		26M	112/68			Normal
46	201	39M	130/76		0.24	Normal
47	177	51M	120/80		0.32	Diabetes mellitus & cardiac decompensation
48	176	45F	115/75		0.29	Diabetes mellitus
49	175	16F	115/65		0.18	Diabetes mellitus
50	171	68M	142/72		0.89	Laennec's cirrhosis
51	105	43M	120/70		0.95*	Normal
52	100	23F	186/80		0.0*	Coarctation of aorta
53	99	23F	110/50		0.0*	Rheumatoid arthritis
54	154	38F	110/60		2.15	Tricuspid insufficiency; mitral stenosis
Mean		36.8			0.35	
			Normals—First Published Series†			
55		24M			0.86	Normal
56		30M			0.28	Normal
57		33M			0.72	Normal
58		36M			1.18	Normal
59		38F			2.85	Normal
60		39M			1.14	Normal
61		42M			0.0	Normal
62		43M			1.7	Normal
63		44M			0.285	Normal
Mean					1.00	

* Pherentasin units represent best estimate of available data which do not fulfill requirements of test by definition given in this paper.

† Pherentasin units represent best estimate from Fraction A of Stock and Schroeder[1] usually on a single assay. This fraction was very crude.

than in the endocrine[5] or neurogenic[6] types of hypertension. Differences in concentration were studied for their relations to these types, to the age of the patient and to the duration of hypertension. No good relationship was seen between age of the patient and the level of pherentasin in the blood (fig. 3). The 45 to 55 year age group included the majority of patients and therefore the range of concentration was greatest in that area. However, the mean value for that group was not much above that of the others tested. Analysis of the duration and type of hypertension (table 1) shows that higher concentrations have been found more frequently in the renal type than in the endocrine and neurogenic groups. The range of values within each group is large, and the test is therefore of only fair diagnostic value for individual cases. The miscellaneous series includes mixtures of the above types as well as those with features complicating hypertension.

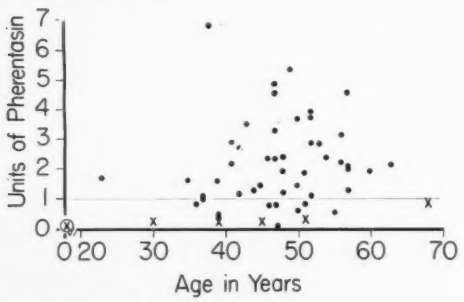


FIG. 3. Age of subject and concentration of pherentasin in blood. Values of less than one unit are considered inactive. The unit of pherentasin is defined in the text. Base age, 16. ●, hypertensive; ×, normotensive.

It is likely that a pure type of hypertension never occurs. The classifications made are based, however, on the clinical judgment of two or more physicians, on laboratory data, and in many cases on tests such as the histamine[6] and sweat tests[5] designed specifically for such differentiation. When proper allowance is made for the potential inaccuracies in both the diagnostic and assay methods, the differences found may be taken as an indication that the type of hypertension is one of the factors controlling the concentration of pherentasin in arterial blood. This was not found to be true of the known duration of hypertension. No correlation between this parameter and units of pherentasin in the blood of hypertensive patients was observed. The possibility remains that some relationship may be found when sufficient factors are controlled.

CHEMICAL STUDIES

Three types of extracts were studied. Extracts of hypertensive blood which proved to be pressor in the rat were pooled and designated "active extract." Hypertensive extracts which were not pressor were called "inactive extract." All blood was treated in the same way except for 520 ml. of the first "normal" pool which was obtained from the blood bank. These pooled fractions will be discussed under the appropriate headings.

Preliminary Tests

Because of the paucity of active material in blood, microchemical technics were used initially to determine whether or not primary amine groups were present. The color reaction with ninhydrin was positive in both test tube and spot tests on paper. Single dimensional paper chromatography was carried out according to the method of Williams and Kirby.[4] When 0.167 ml. of the active extract was run in a phenol-water bath, three spots appeared on spraying with a solution of ninhydrin specially developed for amines.[7] When 0.334 ml. of extract was run in a butanol-water solvent, five spots developed. Several repetitions of this procedure showed the presence of eight amino nitrogen compounds from butanol-water chromatograms and six from phenol chromatograms (table 2). Two-dimensional chromatography,* using collidine and lutidine for one direction and phenol-water for the second, was carried out on 1.0 ml. and resulted in 10 ninhydrin-sensitive spots. Their positions on the paper gave presumptive evidence for the presence of seven amino acids, histamine and two unidentified substances. The presence of amino acids

* The assistance of Dr. Eugene Roberts of the Laboratory of Cancer Research in carrying out the two-dimensional chromatogram is gratefully acknowledged.

indicated incomplete separation of acidic from basic compounds but the presence of two large unidentified spots was taken as evidence for considerable elevation of the ratio of organic base to acid.

More direct evidence for the presence of at least one basic compound† containing a primary amine group was obtained by ion exchange on a second resin, Amberlite IRC-50.‡ A fraction of the active extract representing a few milliliters of original blood was agitated with 30 mg. of the resin for several minutes. The few grains of resin were transferred to a small piece of cellophane and rinsed several times with water. The excess rinse water was blotted off and the amines liberated from the resin by elution with one or two drops of tenth normal hydrochloric acid. On drying, two drops of ninhydrin reagent turned the grains of resin blue. Approximately 20 μg. of alanine treated similarly gave no color.

TABLE 2.—*Mean R_f Values on Paper Chromatography of Pressor Extracts in Butanol and in Phenol*

Butanol (7 Runs)		Phenol (3 Runs)	
No. of Times Substance Appeared	Mean Rf of Substance	No. of Times Substance Appeared	Mean Rf of Substance
7	0.02	2	0.02
2	0.13	2	0.23
3	0.21	1	0.41
2	0.37	1	0.51
3	0.46*	2	0.66
1	0.54*	1	0.72
2	0.61*		
3	0.67*		

Note: The extracts were chromatographed before purification with Amberlite IRC-50.

* These substances are probably primary amines.

Purification and Assay

Paper Chromatography. A larger fraction of the pooled active extract was mixed with resin IRC-50 and both the filtrate and tenth normal hydrochloric acid eluate were run on a butanol-water paper chromatogram for 16½ hours. The filtrate separated into seven amine compounds and the eluate into two (fig. 4). Of the latter, one of the substances barely moved and had an Rf value in the range of histamine, histidine, arginine, and lysine. The second amino compound found in the eluate gave a distinct blue color after spraying and had an Rf of 0.62. As indicated elsewhere[7] this finding strongly suggests the presence of a 5 to 7 carbon aliphatic moiety but does not rule out a ring structure.

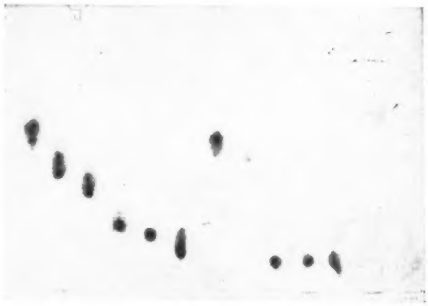


FIG. 4. One-dimensional ascending-paper chromatogram of selected amines, amino acids and pherentasin eluate and filtrate of resin IRC-50. Ninhydrin-sensitive substances and their R_f values from left to right are isoamylamine 0.51, tryptamine 0.38, tyramine 0.30, ethylamine 0.15, arterenol 0.115, histamine 0.06–0.11, phenethylamine 0.47, butylamine 0.43, lysine 0.01, arginine 0.02, histidine 0.02, pherentasin eluate 0.05, 0.62, and pherentasin filtrate 0.02, 0.23, 0.34, 0.44, 0.72. The large spot at bottom of eluate is an artefact resulting from the volume of eluate applied.

However, it favors the absence of phenolic groups in this substance, since all phenolic amines tried have given a yellow to brownish hue. Evidence that this substance may be an abnormal metabolite of at least the renal type of hypertension was obtained when a pool of similarly prepared extracts of normotensive individuals was treated in a similar manner. The only ninhydrin-sensitive substance found was the one with the low Rf value. Identification of the rapidly moving substance with pherentasin is still lacking, although the eluate from IRC-50 was positive in the rat mesoappendix test (table 3).

† Two-dimensional chromatography did not indicate the presence of histidine, lysine, or arginine, the basic amino acids. It did indicate aspartic, glutamic, α-aminobutyric acids and glycine, serine, alanine, and taurine.

‡ The Amberlite IRC-50 resin was obtained through the generosity of Dr. James C. Winters of the Rohm and Haas Company, Philadelphia.

The presence of a ninhydrin-sensitive compound with an Rf of 0.64 in the filtrate of the inactive pool may be evidence for incomplete uptake by the Amberlite IRC-50 resin. This would not be surprising, since very weak bases are taken up poorly by Amberlite IRC-50. The absence of a ninhydrin spot on the phenol-water chromatogram of the eluate of this separation may be taken as further evidence of incomplete ion exchange.

Mesoappendix Test. The Chambers-Zweifach rat mesoappendix test[9] was selected as an extremely sensitive, though nonspecific, method for testing the vasoactivity of the extracts containing pherentasin. It has been shown[3] that all pressor extracts have been positive in the mesoappendix test but the absence of a blood pressure rise in the rat is no sign of lack of vasoactivity. Two interpretations are possible. Pherentasin may be present in such small amounts as to give a negative pressor test. On the other hand, another vasoexcitor which does not necessarily have an effect on blood pressure may be invariably present when pherentasin is present and frequently when it is not. The latter seems unlikely.

Figure 5 shows the results of fractionations and assay procedures on the active and inactive pools of hypertensive blood. The mesoappendix test was positive in both pools. It was also positive in the active eluate and was negative in the inactive filtrate. The filtrate of one treatment of the active pool was negative, but was positive after another treatment. This difference may have been caused by incomplete ion exchange in the latter case.

TABLE 3.— *Fractions of Pherentasin Showing Vasoactivity in Mesoappendix Test*[9]
(0.1 ml. Injected into Tail Vein of Rat)

Prep.*	Dilution of Epinephrine Required		Duration of Response Min.	Remarks
	Control	After		
Active Pool	1:2 million	1:16 million	60	
Inactive Pool	1:6 million	1:20 million	75	
Normal Pool	1:2 million	1:1 million	20	
Active Filtrate #1	1:1.5 million	1:15 million	48	Exposed to resin for 5 hours
Active Filtrate #2	1:2.5 million	No change	—	Exposed to resin for 15 min.
Active Eluate #1	1:1.5 million	1:8 million	18	Exposed to resin for 5 hours
Inactive Filtrate	1:0.5 million	No change	—	Exposed to resin for 15 min.

* Filtrate = Concentrated extract[2] exposed to Amberlite IRC-50.
Eluate = 0.1 N HCl eluate of IRC-50 neutralized.

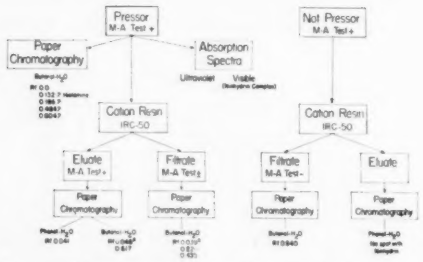


FIG. 5. Diagrammatic outline of isolation and assay procedures of pherentasin extracts of arterial hypertensive blood. M-A refers to mesoappendix test. Spots marked X were very large, probably the result of diffusion of salt present in the extracts. See text.

Absorption Spectra. The ultraviolet absorption spectrum of the active pool indicated peaks at 273 and 320 mm., the absorption densities of which were greatly reduced in an Amberlite IRC-50 eluate of the pool. Figure 6 shows the absorption in the visible range of the color complex formed between ninhydrin and concentrates of pherentasin; isopropanol and 90 per cent ethanol were used as solvents for pherentasin. The pherentasin-ninhydrin solution in isopropanol was slightly turbid and the second peak of the ninhydrin-amine complex (520 μ) occurred at a wave length well below the lowest present in the amines of biologic interest chosen for study.[7] The turbidity was only partially corrected by using 90 per cent ethanol as solvent. Ultraviolet spectra and those of the ninhydrin complex of highly con-

centrated extracts of pherentasin showed definite differences from comparable absorption curves made for methylamine, ethylamine, butylamine, isoamylamine, tyramine, tryptamine, histamine, arterenol, and phenethylamine.

Electron Diffraction. One-tenth ml. of the oil fraction referred to previously[2] was chromatographed in a butanol-water solvent. On spraying with ninhydrin a spot with an Rf of 0.042 developed, indicating histamine or one of the amino acids. A solution of the crystals* was chromatographed on paper in a butanol-water solvent. A narrow vertical strip was cut from the paper along the edge of the pherentasin "crystal extract." A large spot appeared at an

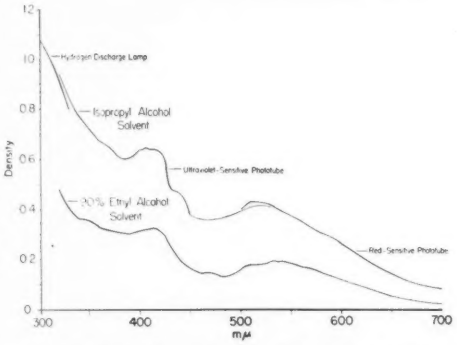


FIG. 6. Absorption spectra of pherentasin-ninhydrin complex. Description in text.

Rf range of 0.0 to 0.15. Another very faint spot was perceptible at approximately 0.5. The unsprayed paper between Rf values 0.0 and 1.0 was cut into 12 squares, the lowest being larger than the rest to accommodate the area apparently taken by the amino compound. Each was made into a mash and eluted with three times normal hydrochloric acid, evaporated to a few drops and dried in a vacuum desiccator.

The eluate from the Rf fraction from 0.0 to 0.15 was photographed under the electron diffraction beam of an RCA model electron microscope on the chance of obtaining additional information on the chemical groups present in the material which does not move in butanol-water. Distinct rings observable in the diffraction patterns of the sample were not present in the collodion blank. The ring diameters did not coincide with any of those for organic compounds listed by the American Society for Testing Materials.

TABLE 4.—*Pressor Response from Volatile Extracts of Arterial Blood*

Blood Sample No.	Sex	Subject's B.P.	Rat Pressor Response*	
			Non-Volatile Pherentasin Fraction	Volatile Fraction
		mm.Hg.		
180	M	Normal	−	−
174	F	240/130	−	−
173	M	190/115	−	−
181	F	195/120	+	−
182	M	185/105	−	+
183	M	210/135	+	+
184	F	194/130	+	+
185	M	250/140	+	+

* Positive response of one unit or more (see text).

Volatile Pressor Substance. Since a search for volatile pressor substances in the blood of hypertensive patients had never been made, the extraction procedure was modified in such a way as to collect any compounds volatile at high pH and room temperature. Before chloroform extraction of the eluate of the Amberlite IR 100 H resin, the pH was raised slowly to pH 10 while air was drawn through the eluate past a trap immersed in acetone-dry ice. While still cold the trapped compounds were dissolved in 2 ml. of 0.15 normal hydrochloric acid. Before assaying, they were neutralized. The results of the assays of eight such fractions are shown in table 4 and compared with the nonvolatile

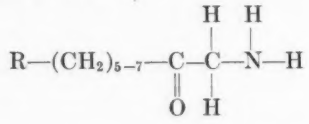
* Five ml. of the active extract were concentrated to 1 or 2 ml. in vacuo, centrifuged, and the supernatant evacuated almost to dryness. Water was added to make 1 ml. and the suspension centrifuged and concentrated again to about 2 drops. On refrigeration and agitation white crystals appeared which dissolved on warming to about 50 C. The above operation was repeated until large crystals separated from an oil. The crystals appeared to be difficultly soluble in acetone, while the oil readily dissolved in acetone. Separation of the oil from the crystals was not quantitative but attempts at determining the pressor activity of each fraction were made. Two injections of the crystal fraction resulted in blood pressure elevations of 14/10 mm. Hg and 16/15 mm. Hg at the end of 25 minutes. Two injections of the oil fraction resulted in a markedly depressor response in one case and no significant effect in the other.

chloroform-soluble fraction of pherentasin. Four of seven volatile fractions were positive. A single normotensive blood was negative in both fractions. These observations suggest the existence of more than one humoral pressor substance.

Discussion

The presence of one or more humoral pressor substances in arterial blood of hypertensive patients not present in normotensive blood extracts prepared similarly is now well established. Preliminary evidence indicates that, in addition to pherentasin, a volatile pressor substance is present in blood of some hypertensive patients, usually those in which pherentasin is found in sufficient concentration to give a pressor response in the rat.

The advances made in knowledge of the chemical nature of pherentasin indicate that the active material separated from most of its contaminants contains at least one primary amine which is not present in normotensive extracts of blood. Evidence that this substance has a 5 to 7 carbon chain attached to the amino group was obtained by paper chromatography. Together with the inactivation by hydroxylamine and semicarbazide,[2] indicating the presence of a carbonyl group, a tentative formula for the active compound can be given:



There is no evidence for the position of the carbonyl group, the nature of R (if any), or the presence or absence of additional nitrogen in the molecule.

The quantitation of the material by pressor assay in the rat has demonstrated its presence in more hypertensive patients than previously realized. Its concentration is not related to age but appears to be generally higher in the renal type. The lack of correlation between concentrations of pherentasin and diastolic blood pressures of the patients is taken as presumptive evidence for the presence of variable amounts of depressor substances in circulating arterial blood of hypertensive subjects. Other alternatives seem much less likely. (a) Variations in a neurogenic pressor mechanism might account for different degrees of vasoconstriction in different patients, compensating for variations in pherentasin level. If true, this should be clearly reflected in the average concentrations in the neurogenic and the renal types of hypertension. Although more pherentasin is usually present in the blood of the renal group, the wide variability of levels requires a larger sampling before significant differences can be established. The neurogenic component, therefore, does not account for the lack of correlation between pherentasin and blood pressure. (b) Variations in the amount of depressor contaminants in the extracts, large enough to mask the concentrations of pherentasin, are an unlikely explanation when such a routine procedure is used. (c) Similarly it is impossible that destruction or loss of the active principle could occur in some of the extractions without occurring in all. The sevenfold range of concentrations of pherentasin observed at the same level of diastolic blood pressure makes any interpretation difficult to accept, other than that there are variable amounts of depressor material in the circulating blood. The possibility remains that pherentasin has a linear relationship with diastolic blood pressure below a certain threshold of nearly maximal effect on arterioles. It will be noted from the case of rheumatic heart disease with mitral stenosis and cardiac decompensation that factors leading to the production of pherentasin can be present without an elevated blood pressure. Other normotensive subjects, however, have been shown to have neither pressor nor vasoexcitor substance in their extracts.[3] The two exceptions were in febrile states. Until its final identification is accomplished, chemical determination of the concentration of pherentasin in blood will not be feasible. Efforts in this direction are now in progress.

Summary

1. Pherentasin, a pressor substance present in human arterial hypertensive blood, has been separated as a base from a number of amino acid and other contaminants.

2. Its partial tentative formula is proposed.

3. The unit of pherentasin is defined statistically and quantitative estimates of its concentration in blood are correlated with various clinical parameters.

4. Evidence for the existence of a volatile pressor substance distinct from pherentasin in arterial blood of hypertensive patients is presented.

ACKNOWLEDGMENTS

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REFERENCES

[1] STOCK, C. C., AND SCHROEDER, H. A.: Pressor substances in arterial hypertension: Activity and amine content of crude extracts of blood. Am. J. Physiol. **2:** 160, 1950.

[2] OLSEN, N. S., AND SCHROEDER, H. A.: Pressor substances in arterial hypertension. III. Chemical studies on pherentasin. J. Exper. Med. **92:** 561, 1950.

[3] SCHROEDER, H. A., AND OLSEN, N. S.: Pressor substances in arterial hypertension. II. Demonstration of pherentasin, a vasoactive material procured from blood. J. Exper. Med. **92:** 545, 1950.

[4] WILLIAMS, R. J., AND KIRBY, H.: Paper chromatography using capillary ascent. Science **107:** 481, 1948.

[5] DAVIES, D. F., AND CLARK, H. E.: A hypertensive syndrome with relative adrenal cortical overactivity. Circulation **2:** 494, 1950.

[6] SCHROEDER, H. A., AND GOLDMAN, M. L.: A test for the presence of "hypertensive diencephalic syndrome" using histamine. Am. J. Med. **7:** 162, 1949.

[7] DAVIES, D. F.: Studies on primary amines. I. Methods. To be published.

[8] — AND SCHROEDER, H. A.: Ninhydrin reaction with amines. Federation Proc. **9:** 28, 1950.

[9] ZWEIFACH, B. W.: Indirect methods for regional blood flow. I. Microscopic observations of circulation in rat mesoappendix and dog omentum: use in study of vasotropic substances. In Methods in Medical Research (V. R. Potter, ed.). Chicago, Year Book Publishers, 1948.

Influence of Thyroidal Function on Vascular Reactivity in Dogs

By IRVINE H. PAGE, M.D., AND JAMES W. MCCUBBIN, M.D.

Responsiveness to several vasoactive drugs has been found to be sharply reduced following suppression of thyroidal function with radioactive iodine, propylthiouracil or surgical thyroidectomy in dogs. The exception was tetraethylammonium chloride, its vasodepressor activity being unchanged or increased with the appearance of the athyroid state. Replacement therapy with desiccated thyroid did not restore vascular reactivity towards normal and produced inversion of adrenaline responses. Myxedema occurred in but 1 of 11 chronically athyroid dogs.

VASCULAR reactivity—or responsiveness—of blood vessels may be measured in several ways. Here it is considered in terms of change in arterial pressure following vasoactive chemical stimuli. The relationship between vascular reactivity and thyroidal function has been studied because of: (1) the well known effects of this function on tissue metabolism; (2) the systolic hypertension and increased cardiac output which occur in Grave's disease; (3) the demonstration by Blumgart, Freedberg and Kurland[1] that hypothyroidism induced by radioactive iodine lessens the work of the heart and presumably the force of its beat; (4) the demonstration by Sawyer and Brown[2] that in hypothyroidism the cardioaccelerator response of the heart to adrenaline is diminished; (5) the fact that many of the signs and symptoms of thyrotoxicosis have been explained on the basis of sensitization of sympathetic nerve endings to adrenergic drugs; (6) the fact that in myxedema, reactivity of the whole organism sinks to a low ebb and it is a reasonable presumption that reactivity of the heart and blood vessels is concurrently impaired.

To this end, vascular reactivity has been evaluated in dogs before and after establishment of hypothyroidism (thyroidectomy, radioactive iodine or propylthiouracil) and then again after feeding thyroid powder. The use of the dog as an experimental animal may be unfortunate in that this species seems to be less dependent on thyroidal activity than most laboratory animals. On the other hand, the majority of previous similar studies of vascular reactivity in experimental hypertensive vascular disease have utilized dogs.

From the Research Division of the Cleveland Clinic Foundation, and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

METHODS

Twelve normal adult mongrel dogs weighing from 8.6 to 14.2 Kg. were used. Arterial pressure was recorded on a smoked drum from a mercury manometer after cannulation of the femoral artery under sodium pentobarbital anesthesia. Heparin was used in the connecting tubing. Test drugs were adrenaline, noradrenaline, histamine and tetraethylammonium chloride (TEAC) given in this order and, with the exception of tetraethylammonium chloride, each repeated once or several times until nearly identical responses were obtained. Angiotonin (5 cat units) and renin were used in some but not all experiments. Injections were made into a femoral vein. Care was taken that doses of test drugs, again with the exception of tetraethylammonium chloride, were submaximal and the same for each dog for the duration of the experiment. Tetraethylammonium chloride was given in a dose of 5 mg. per kilogram of body weight. Testing was done at intervals of several weeks under standardized conditions so that each dog was tested from four to eight times over periods ranging from 4 to 15 months.

Total surgical thyroidectomy was successful in only three animals. The most frequent cause of failure was that the parathyroid implants often carried residual fragments of thyroid tissue which later regenerated. Regeneration was evidenced by fall in blood cholesterol and by cervical uptake of radioactive iodine (I^{131})* several weeks or months

* The radioactive iodine used in this investigation was supplied by Oak Ridge National Laboratory on authorization from the Isotopes Division, U. S. Atomic Energy Commission. We are indebted to Dr. Otto Glasser of the Cleveland Clinic for measuring both therapeutic and tracer doses of radioactive iodine, for his advice on handling the material and for measuring cervical uptake of the tracer doses.

after operation. Consequently, therapeutic doses of I^{131} were used in eight dogs, five of which had had previous unsuccessful surgical attempts at removal of all thyroid tissue. Single doses of 15 to 20 millicuries, given intravenously, completely suppressed thyroidal function as judged by lack of uptake of tracer doses of I^{131} given at regular intervals throughout the course of each experiment. None of these animals developed tetany. Thyroidal function was suppressed in two dogs by feeding propylthiouracil,† 1.2 Gm. in chopped meat daily for four weeks. One of these subsequently received I^{131} and is included in the group above. Cholesterol determinations were done by the Schoenheimer-Sperry method through the courtesy of Dr. Helen Brown.

Results

1. *Hypothyroidism Induced by Thyroidectomy or I^{131}*

Suppression of thyroidal activity by surgical thyroidectomy or I^{131} significantly altered vascular reactivity (tables 1 and 2). Adrenaline and noradrenaline responses were uniformly and often strikingly decreased. Reactivity to histamine varied considerably from test to test in both normal and athyroid dogs; while average responses were decreased in eight dogs, they were unchanged or slightly enhanced in three. Reactivity to tetraethylammonium chloride varied spontaneously from test to test both in normal and athyroid dogs. In the eight animals treated with I^{131}, average hypotensive responses were consistently greater than in control tests. In the three surgically thyroidectomized dogs, responses to tetraethylammonium chloride were either unchanged or slightly decreased. This was the only significant difference between the two groups.

Responses to repeated doses of tetraethylammonium chloride, initially depressor, diminished and were finally pressor in both normal and athyroid dogs. Potentiation of adrenaline and noradrenaline responses by tetraethylammonium chloride occurred in both groups, the percentage increase being the same or greater in athyroid animals.

Responses to angiotonin and renin were greatly depressed in the athyroid state.

Spontaneous variation in responsiveness to adrenaline and noradrenaline from test to test is often found in euthyroid animals.[3] This variability decreased in athyroid animals. Spontaneous change in reactivity was especially marked in one normal dog in which adrenaline and noradrenaline responses increased progressively over 15 weeks. This sequence was interrupted dramatically by administration of 20 millicuries of I^{131} (fig. 1). Responses to adrenaline and noradrenaline were strikingly decreased, reactivity to histamine diminished and responses to tetraethylammonium chloride were usually larger, though there was considerable variation from test to test.

Definite change in reactivity was observed as soon as four weeks after treatment with I^{131} and as soon as two weeks after surgical thyroidectomy. No attempt was made to determine exactly the latent period preceding change in

Table 1.—*Average Vascular Responsiveness in mm. Hg before and after I^{131}*

Dog No.	Condition	Adrenaline	Noradrenaline	Histamine	TEAC
2680	normal	+41	+52	−34	−59
	4½ mos....	+19	+20	−17	−68
2860	normal	+25	+33	−28	−24
	2 mos.....	+19	+14	−33	−33
2431	normal	+44	+82	−30	−40
	3 mos.....	+18	+29	−13	−54
2932	normal	+44	+39	−54	−57
	1½ mos....	+26	+26	−38	−67
2969	normal	+48	+41	−56	−51
	4 mos.....	+21	+30	−50	−64
3003	normal	+38	+31	−20	+6 −23
	3½ mos....	+15	+17	−23	−48
3133	normal	+39	+45	−26	−29
	1½ mos....	+18	+24	−15	−37
3150	normal	+71	+72	−24	−30
	2 mos.....	+28	+28	−9	−66

Table 2.—*Average Vascular Responsiveness in mm. Hg before and after Total Surgical Thyroidectomy*

Dog No.	Condition	Adrenaline	Noradrenaline	Histamine	TEAC
3008	normal	+36	+39	−51	−64
	6 mos. after	+16	+26	−27	−66
2809	normal	+46	+50	−59	−73
	1 mo. after	+28	+26	−38	−25
3167	normal	+48	+41	−44	−56
	3 mos. after	+31	+30	−31	−42

† Propylthiouracil powder was generously supplied by Dr. Kenneth Thompson, Organon, Inc., and Dr. S. M. Hardy, Lederle Laboratories.

reactivity after alteration of thyroidal function. Over an average period of six months athyroid dogs showed no tendency to revert to euthyroid reactivity patterns.

mine was unchanged in one dog and diminished in the other. Responses to tetraethylammonium chloride were moderately increased in both. Biopsy of the thyroid gland at end of propyl-

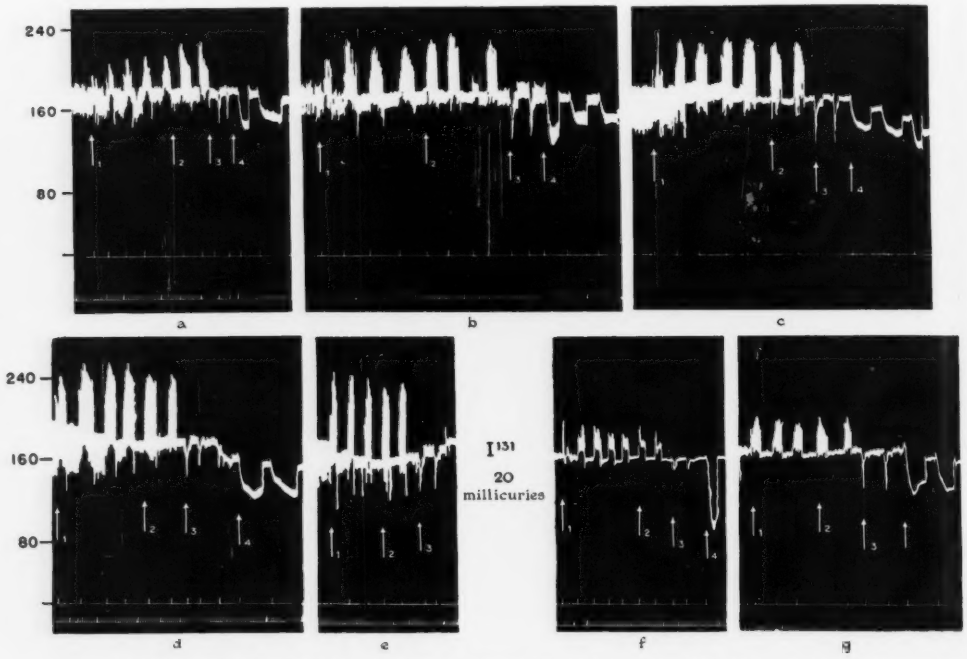

FIG. 1. Spontaneous increase in reactivity to adrenaline and noradrenaline in normal dog followed by treatment with I^{131}. *A*. 4/13/50. *B*. 4/27/50. *C*. 6/7/50. *D*. 7/12/50. *E*. 8/3/50. 9/3/50 I^{131}, 20 millicuries. *F*. 11/8/50. *G*. 12/7/50. (1) Adrenaline. (2) Noradrenaline. (3) Histamine. (4) Tetraethylammonium chloride.

TABLE 3.—*Average Vascular Responsiveness in mm. Hg before and after Propylthiouracil*

Dog No.	Condition	Adrenaline	Noradrenaline	Histamine	TEAC
2860	normal	+25	+33	−28	−24
		+6	+4	−27	−58
2766	normal	+33	+41	−24	−25
		+23	+16	−11	−47

2. *Hypothyroidism Induced by Propylthiouracil*

Two normal dogs received propylthiouracil daily for four weeks. At the end of this time, changes in reactivity closely resembled those seen in I^{131} treated animals (table 3). In one, diminution in reactivity to adrenaline and noradrenaline was more than was later produced by I^{131} in the same animal. Reactivity to histathiouracil feeding showed the characteristic changes consistent with the drug-induced hypofunction.

3. *Serum Cholesterol in Thyroidectomized and I^{131} Treated Animals*

Vascular reactivity changed before there occurred a significant rise in serum cholesterol. No close correlation was found between cholesterol levels and responsiveness. Cholesterol levels fluctuated widely on the standard kennel diet of Purina dog chow supplemented by 1 pound of ground meat three times weekly, but all animals showed significant hypercholesterolemia. Maximum elevations in I^{131} treated dogs were 38, 72, 83, 110, 112, 118, 193, and 290 per cent of respective control values. In thyroi-

dectomized animals, maximum elevations were 82, 126 and 150 per cent.

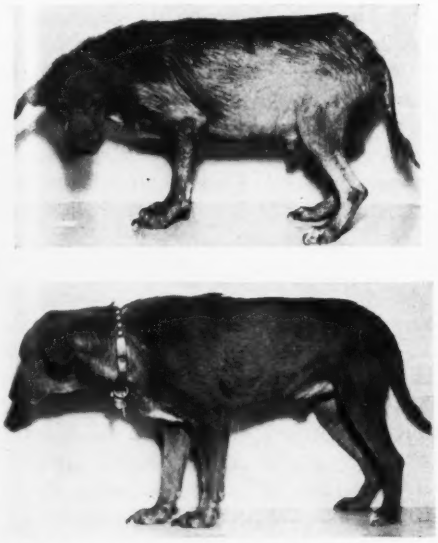

FIG. 2. Myxedema in dog No. 3133 and its improvement with thyroid feeding. *Above.* Eight weeks after receiving 20 millicuries of I^{131}. *Below.* After receiving desiccated thyroid 1 Gm. per kilogram for four weeks.

became thick and edematous and body weight increased by 21 per cent. Other changes were common to the whole group. The hair became coarse, dry and thinned and often fell out in patches over the legs and abdomen. Marked apathy and listlessness were characteristic but appetites remained good and slight to moderate weight gain occurred in six of eight animals treated with I^{131}. None of the thyroidectomized group had a gain in weight and one had a moderate weight loss. Neither thyroidectomy nor I^{131} produced marked change in average arterial pressure.

TABLE 4.—*Vascular Responsiveness in Athyroid Dogs before and after Being Fed Desiccated Thyroid 1 Gm. per Kg. Daily for Four Weeks.*

Dog No.	Condition	Adrenaline	Noradrenaline	Histamine	TEAC
3133	athyroid	+18	+24	−15	−37
		−10	+10	−25	−50
3150	athyroid	+28	+28	−9	−66
		−7	+35	−20	−54
3003	athyroid	+15	+17	−23	−48
		−9	+16	−13	−53

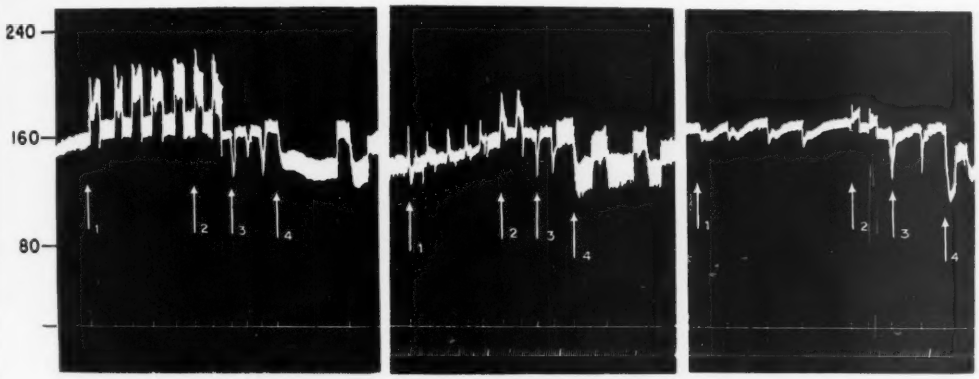

FIG. 3. Typical changes in reactivity pattern with appearance of athyroid state and after replacement therapy. *A.* Normal. *B.* Six weeks after 20 millicuries of I^{131}. *C.* After receiving desiccated thyroid 1 Gm. per kilogram daily for four weeks. (1) Adrenaline. (2) Noradrenaline. (3) Histamine. (4) Tetraethylammonium chloride.

4. *Appearance and Behavior of Athyroid Dogs*

The complete picture of myxedema appeared in only 1 of 11 thyroidectomized or I^{131} treated dogs. This animal, eight weeks after receiving 20 millicuries of I^{131}, developed ascites; the skin

Three dogs made athyroid by I^{131} were fed desiccated thyroid (Parke, Davis USP)* 1 Gm.

* We are grateful to Dr. Harry E. Carnes, Parke, Davis and Co., for a generous supply of desiccated thyroid.

per kilogram of body weight daily and, within three to four weeks, appearance and behavior of all became entirely normal. Recovery was especially characterized by abundant growth of new hair. The one animal showing signs of myxedema was included in this group (fig. 2) Weight returned to normal in all. Subsequent weight loss or other signs of thyrotoxicosis failed to appear, although one dog was fed 1.5 Gm. desiccated thyroid per kilogram of body weight daily for two months.

5. *Influence of Thyroid Feeding on Reactivity in Athyroid Dogs*

Paradoxically, though these dogs were entirely normal in appearance and behavior after treatment with desiccated thyroid, adrenaline responses were further decreased, becoming entirely depressor in all. Reactivity to noradrenaline, histamine and tetraethylammonium chloride was largely unchanged with no consistent trend towards a return to euthyroid reactivity patterns (table 4; fig. 3).

Discussion

The athyroid state in dogs is associated with consistent and striking diminution of vascular responsiveness to adrenaline and noradrenaline. When animals were restored to normal appearance and behavior with large doses of desiccated thyroid, reactivity to noradrenaline remained unchanged. Adrenaline responses, however, became inverted. This seemingly anomalous effect of replacement therapy in athyroid dogs is in accord with a recent report of Riggs, Stanbury and Carr[4] who found that feeding large amounts of desiccated thyroid to normal dogs decreased vasopressor activity of adrenaline.

It is puzzling why the administration of large amounts of thyroid powder failed to restore vascular reactivity to normal. Enough time would appear to have elapsed for the thyroid to exert its full effect. It seems as if the long athyroid period may have caused changes in the heart and blood vessels which were irreversible. Alternatively, there is the possibility that destruction of the thyroid causes the loss of functions not alone replaced by oral thyroid powder. The latter possibility is the more appealing one to us.

The hypotensive action of tetraethylammonium chloride was found to be slightly increased in animals treated with I^{131} or propylthiouracil but was unchanged by surgical thyroidectomy. There were no other significant differences in reactivity patterns between the three groups and the reasons for this slight discrepancy are not now apparent. Replacement therapy with desiccated thyroid in I^{131} treated dogs failed to restore responses to tetraethylammonium chloride to normal.

As concerns tetraethylammonium chloride, the more interesting problem is not the slight increase in depressor responses caused by athyroidism, but rather the fact that, at a time when responses to other drugs are severely depressed, tetraethylammonium chloride exerts full or increased activity. Evidently, transmission of autonomic impulses is independent of thyroidal function, while the response of the peripheral vessels and heart show such dependence. In normal animals, tetraethylammonium chloride causes marked augmentation of the response to many vasoactive drugs.[5, 6] Athyroid dogs exhibit the same phenomenon but to a somewhat increased degree, suggesting that their sluggish reactivity may depend in part at least on increased autonomic inhibition. This must be a minor factor, however, for tetraethylammonium chloride blockade does not usually increase the absolute responses of athyroid dogs to values found in control periods.

Responsiveness to renin and angiotonin was markedly decreased with the appearance of the athyroid state. Reactivity to histamine was generally reduced in all three groups of athyroid dogs but not as consistently or as impressively as adrenaline, noradrenaline and angiotonin. Again, replacement therapy with desiccated thyroid failed to restore responses to euthyroid values.

We had not been aware that myxedema was so difficult to produce in dogs. While there were some changes, such as loss and coarsening of the hair and apathy, only 1 of 11 animals showed the full syndrome. All dogs were tested

for I^{131} uptake and none found, so it does not appear that residual thyroid tissue was responsible. This disposes of the opinion that abundant accessory thyroid tissue accounts for the infrequent appearance of myxedema in the dog after surgical thyroidectomy. These experiments confirm that, unlike man and most animals, the dog is not dependent to a great degree on thyroid hormone and that thyrotoxicosis is produced with great difficulty in the dog by feeding large doses of thyroid powder.[7–9] It is important that these facts be emphasized, for reports often appear concerning animal experiments in which hyper- or hypothyroidism is assumed without stating exactly the condition of the animals that justified this conclusion.

Summary

Vascular responsiveness to adrenaline, noradrenaline, angiotonin, renin, histamine and tetraethylammonium chloride has been measured before and after suppression of thyroidal function by surgical thyroidectomy, I^{131} or propylthiouracil. Attention was called to the difficulty of accomplishing complete surgical thyroidectomy in dogs. Responsiveness to adrenaline, noradrenaline, angiotonin and renin was consistently and markedly reduced in all three groups of athyroid animals. Reactivity to histamine varied widely from test to test in both euthyroid and athyroid dogs but the majority of animals showed a moderate decrease in responsiveness. Average hypotensive responses to tetraethylammonium chloride were slightly greater following treatment with I^{131} or propylthiouracil but were not regularly altered by surgical thyroidectomy. Reactivity patterns in the three groups of athyroid animals were otherwise the same. Blockade of autonomic ganglions with tetraethylammonium chloride in athyroid dogs augmented the response to vasoactive drugs as in normal dogs but to a slightly greater degree. Absolute responses after tetraethylammonium chloride remained less than they had been before suppression of thyroid function. There was no tendency for athyroid dogs to revert to euthyroid reactivity patterns over an average period of six months and for as long as 12 months. No correlation was found between degree of vascular responsiveness and serum cholesterol level. The latter was significantly elevated in all thyroidectomized and I^{131} treated animals.

The full-blown syndrome of myxedema appeared in only one of eight animals treated with I^{131} and in none of the surgically thyroidectomized group. All showed marked apathy and listlessness, lost hair over the legs and abdomen and moderate weight gain occurred in six of eight dogs receiving I^{131}. Thyroidectomized dogs did not gain weight, one having moderate weight loss, but otherwise resembled I^{131} treated animals. Three dogs treated with I^{131}, the one myxedematous animal included, were fed desiccated thyroid. The appearance and behavior of all became entirely normal within three to four weeks. Vascular reactivity was not similarly modified, however. Adrenaline responses were further decreased in all, becoming entirely depressor. Reactivity to noradrenaline, histamine and tetraethylammonium chloride was largely unchanged, there being no definite tendency toward a return to euthyroid reactivity patterns with replacement therapy. Thyroid replacement therapy did not elicit hyperthyroidism.

Conclusions

Vascular responsiveness to a variety of pressor and depressor drugs in dogs is, in some degree, dependent on activity of the thyroid gland. Failure of this glandular function leads to depression of vascular reactivity to several vasoactive drugs, but not to tetraethylammonium chloride, the effect of which is even enhanced. The conductance of vasomotor impulses by sympathetic ganglions seems largely independent of thyroidal function. Responses to vasoactive drugs are not restored by feeding desiccated thyroid.

Minor degree of clinical hypothyroidism can be produced readily in dogs but myxedema is infrequent. The dog is unusual in that it is relatively insensitive to both excess and deficit of thyroidal hormone.

A possible mechanism explaining the beneficial effects of suppression of thyroidal activity

in man is that, as in dogs, vascular reactivity is sharply reduced and the vascular tree no longer over-reacts to the normal impacts of life.

REFERENCES

[1] BLUMGART, H. L., FREEDBERG, A. S., AND KURLAND, G. S.: Hypothyroidism produced by radioactive iodine (I^{131}) in the treatment of euthyroid patients with angina pectoris and congestive heart failure. Circulation **1:** 1105, 1950.

[2] SAWYER, M. E. MACK., AND BROWN, M. G.: The effect of thyroidectomy and thyroxine on the response of the denervated heart to injected and secreted adrenine. Am. J. Physiol. **110:** 620, 1935.

[3] PAGE, I. H., AND TAYLOR, R. D.: Variations of vascular reactivity in normal and hypertensive dogs. Am. J. Physiol. **156:** 412, 1949.

[4] RIGGS, D. S., STANBURY, J. B., AND CARR, E. A., JR.: The influence of hyperthyroidism on the response to epinephrine in the dog. J. Pharmacol. & Exper. Therap. **101:** 31, 1951.

[5] PAGE, I. H., AND TAYLOR, R. D.: Mechanism of renin tachyphylaxis—restoration of responsiveness by tetraethyl ammonium ion. Science **105:** 622, 1947.

[6] —, AND —: Augmentation of vasoactive substances by tetraethylammonium chloride. Circulation **1:** 1233, 1950.

[7] GLOCK, G. E.: Effects of administration of thiouracil to dogs. Endocrinology **6:** 6, 1949.

[8] CARLSON, A. J., ROOKS, J. R., AND MCKIE, J. F.: Attempts to produce experimental hyperthyroidism in mammals and birds. Am. J. Physiol. **30:** 129, 1912.

[9] DANOWSKI, T. S., MAN, E. B., AND WINKLER, A. W.: Tolerance of normal, thyroidectomized and of thiourea or thiouracil treated dogs to oral desiccated thyroid and to intravenous thyroxine. Endocrinology **38:** 230, 1946.

Effect of Athyroid State on Vascular Reactivity and Arterial Pressure in Neurogenic and Renal Hypertensive Dogs

By JAMES W. McCUBBIN, M.D., AND IRVINE H. PAGE, M.D.

Since vascular responsiveness to adrenaline, noradrenaline, renin and angiotonin is reduced by suppression of thyroidal function in normotensive dogs, it was a possibility that in neurogenic and renal hypertensive animals suppression of thyroidal function might be associated with decrease in arterial pressure. This possibility was not confirmed, hypertension persisting unaltered in both groups of hypertensive animals over long periods of observation. Changes in vascular reactivity were slight in comparison with those associated with the athyroid state in normotensive dogs.

IN THE preceding paper it was shown that complete suppression of thyroidal function in normal dogs sharply reduces vascular responsiveness to adrenaline, noradrenaline, renin and angiotonin. The renin-angiotonin renal pressor system has often been suggested as part of the mechanism of experimental renal hypertension. Adrenaline and noradrenaline are important mediators of the effector portion of the sympathetic nervous system and are, therefore, presumably involved in the mechanism of experimental neurogenic hypertension.

Arterial pressure might be lowered if responsiveness to substances participating intimately in the mechanism of a specific type of hypertension should be reduced. To this end, thyroidal activity has been suppressed with radioactive iodine or thyroidectomy in neurogenic as well as renal hypertensive dogs. The latter group has been included despite previous observations that subtotal[1] or total[2] thyroidectomy has no effect on arterial pressure in dogs with renal hypertension. In view of the difficulty associated with permanent removal of all thyroid tissue[3] it seemed worthwhile to confirm this observation through the use of radioactive iodine.

METHODS

Normal adult mongrel dogs were used in all experiments. Renal hypertension was induced by Page's method[4] and chronic neurogenic hypertension elicited by section of the buffer nerves according to the technic described by Grimson.[5] Blood pressures were measured twice weekly for the first two or three months of each experiment and once weekly thereafter. All pressures were taken in a soundproofed room and recorded from a mercury manometer, after direct puncture of the femoral artery with a 20 gage needle. Pulses were counted by palpation of the opposite femoral artery.

Vascular reactivity was measured according to the technic previously described.[3] Test drugs were submaximal doses of adrenaline, noradrenaline and histamine and were kept the same for each animal for the duration of the experiment. Tetraethylammonium chloride (TEAC) was given in a dose of 5 mg. per kilogram. Reactivity was tested after the establishment of sustained hypertension and again several months after intravenous administration of radioactive iodine (I^{131})* or thyroidectomy. Fifteen to 20 millicuries of I^{131}, given in a single dose, effectively abolished thyroidal function as judged by lack of cervical uptake of tracer doses given at intervals during the course of each experiment. Thyroidectomized dogs failed to show cervical uptake of tracer doses of I^{131}.

RESULTS

A. *Effect of Athyroidism on Experimental Neurogenic Hypertension*

Five neurogenic hypertensive dogs were treated with I^{131} and thyroidectomy was done in another. As seen in table 1, suppression of thyroidal function had no significant effect on

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* The radioactive iodine used in this investigation was supplied by Oak Ridge National Laboratory on authorization from the Isotopes Division, U. S. Atomic Energy Commission. We are grateful to Dr. Otto Glasser of the Cleveland Clinic for his assistance in measuring and handling this material.

arterial pressure over periods ranging from 4 to 17 months with an average of 11.5 months. It was not unusual, however, for arterial pressure to fall to normal or near normal levels during the first few days after administration of I^{131}. This brief hypotensive response was presumably associated with the thyroiditis that follows a large dose of I^{131}. Cardioacceleration, a prominent feature of experimental neurogenic hypertension, was less prominent several months after treatment with I^{131} (table 1).

TABLE 1.—*Arterial Pressure and Pulse Rate in Experimental Neurogenic Hypertension before and after Suppression of Thyroidal Function.*

Dog No.	Control Values		After Suppression of Thyroidal Function			
	B. P.	Pulse	Months	B.P.	Pulse	Procedure
3197	235	185	10	220	140	I^{131}
2814	210	185	17	240	152	I^{131}
2897	205	174	17	225	140	I^{131}
2725	212	164	4	215	142	Thyroidectomy
2717	205	175	13	220	154	I^{131}
3191	242	176	8	215	142	I^{151}

TABLE 2.—*Vascular Reactivity in Neurogenic Hypertensive Dogs before and after Suppression of Thyroidal Function.*

Dog No.	Adrenaline	Noradrenaline	Histamine	TEAC
3197				
control	+35	+65	−48	−92
11 months after I^{121}	+16	+20	−38	−95
2725				
control	+8	+51	−106	−134
4 months after thyroidectomy	+10	+20	−93	−130
3191				
control	+30	+46	−80	−101
8 months after I^{131}	+40	+54	−80	−103
2717				
control	+1	+32	−54	−103
11 months after I^{131}	+15	+20	−40	−91
2814				
control	+2	+24	−63	−83
5 months after I^{131}	+18	+24	−84	−95
2897				
control	+44	+40	−48	−102
10 months after I^{131}	+26	+22	−55	−98

Changes in vascular reactivity after suppression of thyroidal function were minor and equivocal (table 2) in contrast with those associated with athyroidism in normal animals.[3] Pressor activity of adrenaline was more often increased than decreased. Noradrenaline responses were reduced in four dogs, unchanged in one and increased in another. Reactivity to histamine and tetraethylammonium chloride were largely unchanged, the enhanced responsiveness that occurs after buffer nerve section[6] persisting in the athyroid state.

One athyroid neurogenic hypertensive dog received 1 Gm. per kilogram of desiccated thyroid (Parke, Davis USP)* daily for one month. Tested again at the end of this time, adrenaline responses had become entirely depressor. Noradrenaline and histamine responses were unchanged and tetraethylammonium chloride produced a smaller hypotensive response. Replacement therapy did not change arterial pressure or heart rate.

TABLE 3.—*Arterial Pressure and Pulse Rate in Experimental Renal Hypertension before and after Suppression of Thyroidal Function.*

Dog No.	Control Values		After Suppression of Thyroidal Function			
	B. P.	Pulse	Months	B. P.	Pulse	Procedure
3533	195	122	10	200	120	I^{121}
2661	210	110	8	200	104	Thyroidectomy
2700	195	108	7	190	98	Thyroidectomy
3539	190		5	225		I^{131}

B. *Effect of Athyroidism on Experimental Renal Hypertension*

Four renal hypertensive dogs showed no significant change in arterial pressure during observation periods ranging between 5 and 10 months after treatment with I^{131} in two and thyroidectomy in two (table 3).

There was no definite change in reactivity to adrenaline, noradrenaline or histamine. Hypotensive responses to tetraethylammonium chloride were considerably increased in three dogs and were unchanged in the fourth (table 4).

Appearance of both groups of athyroid hypertensive animals was the same as that described for normal dogs following suppression

* Desiccated thyroid was kindly supplied by Dr. Harry E. Carnes, Parke, Davis and Co.

of thyroidal activity. Myxedema appeared in none.

TABLE 4.—*Vascular Reactivity in Renal Hypertensive Dogs before and after Suppression of Thyroidal Function.*

Dog No.	Adrenaline	Noradrenaline	Histamine	TEAC	
3533					
control	+55	+40	−40	+5	−59
9 months after I^{131}	+47	+32	−32		−93
2661					
control	+26	+76	−71	+8	−16
9 months after thyroidectomy	+38	+76	−62		−33
2700					
control	+37	+57	−77		−10
7 months after thyroidectomy	+27	+26	−63		−33
3539					
control	+51	+47	−50		−70
6 months after I^{131}	+54	+48	−56		−74

DISCUSSION

Since reactivity to adrenaline, noradrenaline, renin and angiotonin decreased markedly in athyroid dogs,[3] it seemed reasonable to assume that suppression of thyroidal activity might be of benefit in experimental hypertensions. This study has shown such an assumption to be unjustified. Hypertension persisted to the same or greater degree in both neurogenic and renal hypertensive dogs many months after complete suppression of thyroidal function with I^{131} or after thyroidectomy. On the other hand, it was expected that changes in vascular reactivity associated with athyroidism would occur to the same extent as in normal dogs. This was also not the case. In contrast to normal dogs, athyroidism was associated with only minor and equivocal alterations in vascular responsiveness. With the possible exception of noradrenaline responses which were more often decreased than not, reactivity in neurogenic hypertensive dogs was essentially unchanged. Three of four renal hypertensive dogs showed increased responsiveness to tetraethylammonium chloride as the only change in reactivity following appearance of athyroidism. With these exceptions, it appears that inherent in the mechanisms of both experimental neurogenic and renal hypertension is a tendency to stabilize vascular reactivity at a fixed level which eliminates the modifying effect of suppression of thyroidal function. Even so, reactivity to noradrenaline was sharply depressed in several athyroid neurogenic hypertensive dogs without modifying arterial pressure levels. Also, replacement therapy with desiccated thyroid resulted in complete inversion of adrenaline responses without modifying the hypertensive arterial pressure. It has been shown[5] that neurogenic hypertension depends upon an intact sympathetic nervous system. If adrenaline and noradrenaline are the principal humoral mediators of sympathetic nerves, it is puzzling why diminishing reactivity to these drugs fails to lower arterial pressure in experimental neurogenic hypertension.

As an incidental observation, it was noted that pulse rate in neurogenic hypertensive dogs showed a definite tendency to slow several months after suppression of thyroidal function. Whether this was due to training or to absence of thyroidal function was not determined. The latter view is the more probable one since control periods lasted as long as three months. Despite slower rates, there was no associated fall in arterial pressure and this observation is in accord with a previous report[7] demonstrating the minor role of cardioacceleration in chronic neurogenic hypertension in dogs.

SUMMARY AND CONCLUSIONS

Elimination of thyroidal function by thyroidectomy or treatment with I^{131} failed to modify arterial pressure levels in neurogenic and renal hypertensive dogs over periods of observation as long as 17 months in the neurogenic group and 10 months in the renal group. Slowing of pulse rate in neurogenic hypertensive dogs occurred several months after suppression of thyroidal function without accompanying decrease in arterial pressure.

Athyroidism was associated with only minor changes in vascular reactivity in both groups of hypertensive animals. These were less marked and not as consistently present as in the athyroid state in normotensive dogs.[3] It is suggested that the mechanisms producing experimental neurogenic and renal hypertension

tend also to maintain vascular reactivity at a fixed level. Neurogenic hypertension persisted to the same degree, however, in the face of diminished reactivity to both adrenaline and noradrenaline.

REFERENCES

[1] KATZ, L. N., FRIEDMAN, M., RODBARD, S., AND WEINSTEIN, W.: Observations on the genesis of renal hypertension. Am. Heart J. **17:** 334, 1939.

[2] GLENN, F., AND LASHER, E. P.: Effect of total thyroidectomy upon the production and maintenance of experimental hypertension. Proc. Soc. Exper. Biol. & Med. **38:** 158, 1938.

[3] PAGE, I. H., AND MCCUBBIN, J. W.: Influence of thyroidal function on vascular reactivity in dogs. Circulation. This issue.

[4] —: The production of persistent arterial hypertension by cellophane perinephritis. J. A. M. A. **113:** 2046, 1939.

[5] GRIMSON, K. S.: The sympathetic nervous system in neurogenic and renal hypertension. Arch. Surg. **43:** 284, 1941.

[6] PAGE, I. H., AND MCCUBBIN, J. W.: The pattern of vascular reactivity in experimental hypertension of varied origin. Circulation **4:** 70, 1951.

[7] MCCUBBIN, J. W., AND PAGE, I. H.: Role of cardioacceleration in chronic experimental neurogenic hypertension. Am. J. Physiol. **166:** 12, 1951.

The Relationship of Serum Lipoproteins to Atherosclerosis in the Cholesterol-Fed Alloxanized Rabbit

By FRANK T. PIERCE, JR., M.D.

The alloxanized rabbit fed cholesterol develops extreme hyperlipemia and hypercholesteremia and yet develops a lesser degree of atherosclerosis than does the normal animal fed cholesterol. The concentrations of the S_f 12–30 and S_f 20–30 classes of lipoproteins correlate well with atherosclerosis as finally observed in the alloxanized rabbit, whereas both free and total serum cholesterol correlate negatively with atherosclerosis. In the alloxan-diabetic rabbit, the serum cholesterol is principally carried in the S_f 80–100 and greater classes of lipoproteins, and a metabolic block in the conversion of these lipoproteins to those of S_f 40 and less can be demonstrated.

USING THE analytic ultracentrifuge, Gofman and co-workers[1, 2] have identified several classes of giant, cholesterol-bearing lipoproteins in the serum of humans, rabbits, and other animals. One class of these molecules, designated as the S_f 10–20 class,* has been correlated with atherosclerosis in humans,[3] and a corresponding S_f 10–30 class has been observed to be associated with atherosclerosis in the rabbit.

A normal rabbit has a negligible concentration of all of these classes of lipoproteins in its serum, with the exception of the S_f 3–12 class. A small quantity of lipoproteins of this class has been found in every normal rabbit studied.

As a normal rabbit is fed cholesterol, the lipoproteins of the S_f 3–12 class increase progressively in concentration until a critical value is reached (which varies from rabbit to rabbit). At this time lipoproteins of successively higher S_f class begin to appear; for instance, the S_f 12–20 class appears in the serum, and after a critical concentration of this class is achieved, the S_f 20–30 class begins to appear.[1, 3] Finally, the entire spectrum of lipoproteins is present in large quantity from chylomicrons (approximately S_f 40,000) to the original S_f 3–12 class. Naturally, these divisions of the spectrum of lipoproteins are necessarily arbitrary.

In the original reports by Gofman and associates the S_f 10–30 and S_f 3–10 classes were evaluated as to their relationship with atherosclerosis in the rabbit. Since that time a few normal rabbits have been found whose lipoproteins possess an S_f value of 10. In order to exclude these normally occurring lipoproteins from those developing in the rabbit following cholesterol feeding or other experimental procedures, this normal class will be denoted as the S_f 3–12 class, and consequently in the S_f 12 and greater classes of molecules, no overlap will be obtained with these normally occurring lipoproteins.

Duff and McMillan[4] and Duff and Payne[5] have pointed out the extreme turbidity and the marked elevation of serum cholesterol in the alloxan-diabetic rabbit fed cholesterol, and they have shown further that atherosclerosis is inhibited in spite of this elevation of cholesterol. This observation invites investigation of experimental atherosclerosis in these animals

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* One S_f unit represents a flotation rate of 1×10^{-13} cm. per second per dyne per Gm in a sodium chloride solution of density 1.063 Gm per cc. at 26 C. The lipoproteins were previously isolated from other serum proteins (and high density lipoproteins) by a preparative ultracentrifuge. Spinco Model L and Model E ultracentrifuges were used.

that appear to be partly immune to the atherogenicity of elevated serum cholesterol levels.

Methods

Adult rabbits of both sexes of the New Zealand White strain were used. The animals weighed between 2.0 and 3.0 Kg. at the start of the experiment and received a diet of Albers "Family Style" rabbit pellets and water given ad libitum.

Alloxan monohydrate (Eastman Kodak Co.) was administered intravenously, using a single dose of 200 mg. per kilogram of a 5 per cent aqueous solution. Fifteen cc. of a 15 per cent solution of glucose in water were given subcutaneously at the end of the alloxan administration, and every four hours thereafter for four subsequent injections. The glucose was necessary to counteract the acute and transient hypoglycemia following alloxan administration. Thirty rabbits were alloxanized in this fashion, and two weeks elapsed before cholesterol feeding was begun. At the end of this two week period, 18 animals had survived, all except two with elevated blood glucose levels in the range of 300 to 600 mg. per 100 cc.

Control blood specimens were obtained at this time, and cholesterol feeding was begun. The cholesterol was dissolved in Wesson oil (1 Gm. in 8 cc.) by gentle heating, and mixed with rabbit food to make a 1 per cent cholesterol-containing mixture. The rabbits were given this food ad libitum and continued on it until the end of the experiment.

Blood specimens were obtained every two weeks and analyzed for sugar by the Folin-Wu method, for free and total cholesterol* by a modification of the Schoenheimer-Sperry method, and for lipoproteins by the ultracentrifugal methods described by Gofman and his co-workers. The concentrations of the S_f 3–12, 12–20, 12–30, 12–40, 20–30, 20–40, 30–40, 40–80, 100–200, 200–300, 300–400, and 100–400 classes of lipoproteins were studied. In this manner a test of the relationship of individual classes of lipoproteins with atherosclerosis could be made.

At the end of 11 weeks all animals were sacrificed by air embolism, and the degree of aortic atherosclerosis determined. The atherosclerosis was graded on an arbitrary scale of 1 plus (least severe) to 5 plus (most severe), with 0 indicating no atherosclerosis macroscopically present.

Results and Discussion

Table 1 shows the original control levels of lipoproteins and cholesterol in this group of alloxanized animals. Several of these rabbits show high control levels of various classes of lipoproteins and cholesterol. This is a result of the transient lipemia and hypercholesteremia produced by acute alloxan toxicity. This lipemia has been investigated by Duff and Wilson[6] and Payne and Duff,[7] who reported it to disappear in three to six weeks in most rabbits. These authors followed alloxanized rabbits on a normal diet for periods as long as one year and report that no atherosclerosis was observed during that time. Since these control data were obtained two weeks after the administration of alloxan, table 1 illustrates the classes of lipoproteins produced by this drug which reflect the transient hyperlipemia and hypercholesteremia.

Table 2 shows the levels of the various classes of serum lipoproteins, cholesterol, and glucose in the alloxanized rabbit fed cholesterol, as well as the degree of atherosclerosis present at the termination of the experiment. Each figure in this table represents the mean of the five readings obtained at two week intervals for the 11 week period of study. The levels of lipoproteins remained relatively constant during the period of 2 to 10 weeks cholesterol feeding. The original control readings were not included, and in this way the mean levels of the various classes of lipoproteins and cholesterol during the period of atherogenesis are presented.

Two animals died* during the 11 week period of cholesterol feeding, and these are excluded from this series. Three animals became alloxan-resistant, and it is interesting to note that these animals all developed severe atherosclerosis. In the remaining 13 animals with persistent hyperglycemia, a range of atherosclerosis from 0 to 5 plus was observed. Tests of the relationship of atherosclerosis to lipoproteins or cholesterol were made for the 16 animals which survived the 11 week period of cholesterol feeding.

Table 3 represents correlation coefficients (Pearson r) between each class of lipoproteins, cholesterol, and atherosclerosis. It is apparent that under these experimental conditions extraordinarily good correlation exists between the over-all 12–40 class of lipoproteins and

* The author wishes to thank David Colman and Virgil Herring for the cholesterol determinations.

* From multiple abscesses and pneumonitis, presumably the sequelae of alloxanization.

atherosclerosis, and individually for the 12–20, 20–30 and 30–40 classes. Intercorrelations being very good correlation between the S_f 12–20 and S_f 20–30 classes. The positive inter-

TABLE 1. *Initial levels of lipoproteins, cholesterol, and glucose in the blood of rabbits two weeks after alloxan injection and before cholesterol feeding was begun. Values of liproproteins and cholesterol are expressed in terms of mg. per 100 cc. of serum, while glucose is expressed in mg. per 100 cc. of whole blood.*

Rabbit	Lipoproteins (Sf)												Cholesterol		Glucose
	3–12	12–20	12–30	12–40	20–30	20–40	30–40	40–80	100–200	200–300	300–400	100–400	Free	Total	
1	18	20	38	49	18	29	11	46	4	0	0	4	—	43	360
2	55	31	42	64	11	33	22	31	7	0	0	7	10	66	385
3	113	19	19	38	0	19	19	0	0	0	0	0	20	78	380
4	18	18	31	51	13	33	20	15	7	0	4	11	6	49	438
5	13	15	35	61	20	46	26	46	13	4	4	21	—	85	488
6	9	9	22	33	13	24	11	59	20	0	0	20	—	82	425
7	35	29	42	62	13	33	20	42	4	0	0	4	—	—	365
8	37	37	63	83	26	46	20	37	9	0	0	9	—	86	350
9	33	11	15	20	4	9	5	0	0	0	0	0	—	—	405
10	29	26	35	48	9	22	13	33	7	0	0	7	9	67	135
11	35	33	46	73	13	40	27	44	13	0	0	13	—	—	425
12	48	20	20	29	0	9	9	18	4	0	0	4	—	58	310
13	48	29	42	60	13	31	18	13	4	0	0	4	—	—	188
14	66	31	35	33	4	4	0	11	0	0	0	0	5	65	375
15	11	18	36	64	18	46	28	110	101	20	0	121	31	135	558
16	11	13	22	33	9	20	13	13	2	0	0	2	—	40	475

TABLE 2.—*Levels of lipoproteins, cholesterol, and glucose in the alloxanized rabbit fed cholesterol. The lipoproteins and cholesterol are expressed in terms of mg. per 100 cc. of serum, the glucose in terms of mg. per 100 cc. of whole blood. Each value represents the mean of five determinations performed at 2, 4, 6, 8, and 10 weeks during the 11 week period of cholesterol feeding. The degree of atherosclerosis found at the end of the 11 week period of study is also included.*

Rabbit	Lipoproteins (Sf)												Cholesterol		Glucose	Deg. of Atherosclerosis
	3–12	12–20	12–30	12–40	20–30	20–40	30–40	40–80	100–200	200–300	300–400	100–400	Free	Total		
1	194	343	1010	1540	667	1197	530	1652	1146	598	517	2261	706	3633	425	2
2	213	433	1463	2204	1030	1771	741	1808	1010	592	385	1987	744	3456	437	4
3	559	755	1842	2525	1087	1770	683	1410	752	449	265	1466	853	4257	394	2–3
4	106	345	793	1048	448	703	255	651	395	310	145	850	355	1804	346	3–4
5	202	143	260	541	117	398	281	1133	3175	3864	2625	9664	1645	6800	459	1–2
6	212	94	159	316	65	222	157	1148	2257	2794	2335	7386	1633	7817	408	1
7	361	667	1664	2277	997	1610	613	1254	669	400	273	1342	694	3262	237	4–5
8	597	196	464	746	268	550	282	1433	3597	3586	2981	10164	1402	6724	389	1
9	499	502	1137	1742	635	1240	605	1883	1870	963	561	3394	852	4538	413	4
10	215	537	1228	1540	691	1003	312	497	191	97	46	334	435	1948	117*	4–5
11	178	284	904	1465	620	1181	561	1489	1069	728	292	2089	788	4394	410	5
12	343	715	1936	2358	1221	1643	422	1307	719	447	290	1456	741	3638	154*	5
13	328	387	1183	1815	796	1428	632	1817	852	532	310	1694	747	3914	380	4
14	180	746	1663	1932	917	1186	269	818	735	469	224	1428	599	3101	198*	4–5
15	158	105	135	202	30	97	67	167	587	614	367	1568	220	709	568	0
16	326	264	772	1243	508	979	471	1714	1012	860	453	2325	801	4002	514	2–3

* Animals in which the blood sugar dropped to 125 mg. per 100 cc. or less during the last two determinations. These animals were classed as alloxan resistant.

tween the various classes of lipoproteins were also performed, as indicated in table 3, showcorrelations of the S_f 20–30 class with other classes above 30 become progressively di-

minished until they finally become significantly negative above S_f 100. From the data on the correlation of the S_f 20–30 and S_f 30–40 classes of lipoproteins and atherosclerosis, and the intercorrelation of these two groups, the measured correlation of the S_f 30–40 class of lipoproteins with atherosclerosis is, at least in part and perhaps wholly, a reflection of the coexisting intercorrelation with the S_f 12–20 and 20–30 classes of molecules.

It can also be seen that the normally occurring S_f 3–12 class of lipoproteins has no significant correlation with atherosclerosis, while the classes of molecules between S_f 100–400 show a significant negative correlation with atherosclerosis. This latter observation had been anticipated since those rabbits with cholesterol is carried principally in S_f classes of molecules above 100, and since the data presented herein indicate that these molecules are not associated with the atherosclerosis process, these animals have high serum cholesterol levels and little atherosclerosis.

Experimental work along other lines in this laboratory suggests that molecules of very large flotation rates, including chylomicrons, are progressively transformed into molecules of successively lower S_f rates until the normally present S_f 3–12 class is reached. It would appear that alloxanized animals have a metabolic block which slows progressive transformations of the lipoproteins, and that this block is such that it produces an accumulation of molecules mostly above S_f 100 in

TABLE 3.—*Correlation coefficients (Pearson r) between the various classes of lipoproteins and cholesterol versus degree of atherosclerosis in the alloxan-diabetic rabbit fed cholesterol. The correlations between total cholesterol and several classes of lipoproteins are also presented. The correlations between the S_f 20–30 class of lipoproteins (which possess the highest correlation with atherosclerosis) and other classes of lipoproteins and total cholesterol are tabulated, as are several other intercorrelations between different classes of lipoproteins. The data in this table were calculated from table 2.*

	3-12	12-20	12-30	12-40	20-30	20-40	30-40	40-80	100-200	200-300	300-400	100-400	Cholesterol	
													Free	Total
Atherosclerosis	−0.06	0.70	0.76	0.76	0.77	0.74	0.54	0.23	−0.52	−0.60	−0.63	−0.59	−0.39	−0.30
Total Cholesterol	—	−0.33	—	—	−0.30	—	—	0.44	0.83	0.82	0.82	0.83	—	—
S_f 20-30	—	0.90	0.99	—	—	—	0.72	0.36	−0.54	−0.65	−0.63	−0.61	—	−0.30

12–30 with 30–40: 0.64 12–20 with 20–40: 0.81 12–40 with 40–80: 0.43

lesser degrees of atherosclerosis tend to have the most turbid serum, and molecules of S_f species above 80–100 are intensely light scattering. The presence of these classes of molecules, therefore, is associated with marked visual lipemia.

In these animals the free and total cholesterol values correlate negatively with atherosclerosis. The final cholesterol levels in several of these animals exceeded 10,000 mg. per 100 cc., and it is of interest to determine in what classes of lipoproteins this immense amount of cholesterol is to be found. The correlations between total serum cholesterol and S_f 100–400 class of lipoproteins are very high, while with the S_f 12–20 and S_f 20–30 classes, cholesterol is negatively correlated. Apparently then, in the alloxan-diabetic rabbit fed cholesterol,

TABLE 4.—*Degree of aortic atherosclerosis found in the normal rabbit after feeding cholesterol. (+ represents least severe and 5+ represents most severe atherosclerosis.)*

Rabbit No.	Weeks of cholesterol feeding			
	4	6	8	10
21	+			
22	++			
23		++++		
24		++++		
25			++++	
26			++++	
27				++++
28				+++++
29				+++++

contrast to the accumulation of molecules primarily below S_f 40 ordinarily seen in the normal rabbit fed cholesterol. The alimentary

lipemia continues to accumulate until vast quantities of molecules above S_f 100 are in the serum.

The disturbance of lipid metabolism induced by alloxanization induces high concentrations of a large number of atypical serum lipoproteins above S_f 100. Much smaller amounts of the S_f 12–30 class, which is correlated with the atherosclerotic tendency, are present.

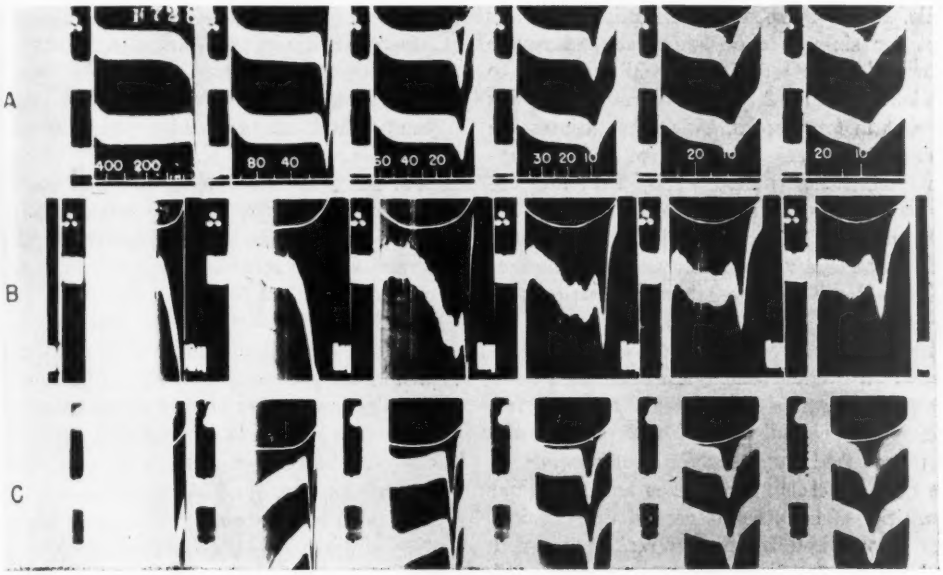

FIG. 1. *A*. Ultracentrifugal flotation pattern in two normal rabbits showing the small peak in the S_f 3–12 region and negligible quantities of lipoproteins of other species. In all the figures, successive frames are taken at 0, 6, 12, 22, 30, and 38 minutes after the ultracentrifuge rotor has reached full speed (52,640 revolutions per minute). Consequently, the S_f markings in these patterns can be used on corresponding frames in the other patterns. In these patterns the lipoproteins of 5 cc. serum were concentrated into 1 cc. by preparative ultracentrifugation and then analyzed in the ultracentrifuge as described above. The solid line drawn in on the top patterns of each photograph represents the baseline of an equivalent salt solution, and the area between this line and the pattern is proportional to the quantity of any class of lipoproteins being measured.

B. Ultracentrifugal flotation pattern in a normal rabbit fed cholesterol and Wesson oil for two weeks. Total serum cholesterol at this time was 1536 mg. per 100 cc. Note the high concentration of S_f 12–30 lipoproteins in this animal. In this pattern the lipoproteins from 2 cc. serum were concentrated into 1 cc. by preparative ultracentrifugation and then analyzed in the ultracentrifuge.

C. Ultracentrifugal flotation pattern in two alloxan-diabetic rabbits fed cholesterol and Wesson oil for 10 weeks. The serum cholesterol at this time was 7440 mg. per 100 cc. in the animal represented by the top pattern, and 10,120 mg. per 100 cc. in the animal represented by the bottom pattern. The turbidity boundary seen in the S_f 80 region reflects the enormous quantities of lipoproteins above this flotation rate in the serum. Note in both patterns the very low concentration of S_f 12–30 lipoproteins, in marked contrast to the normal rabbit fed cholesterol (pattern *B*). In these patterns the lipoproteins from 0.5 cc. of serum were concentrated into 1 cc. by preparative ultracentrifugation and then analyzed in the ultracentrifuge as described above.

The normal rabbit when fed cholesterol develops a hypercholesteremia, and the extra burden of serum cholesterol is mainly carried in the S_f 12–30 classes.[1, 3] This is the explanation for the general association of hypercholesteremia with atherosclerosis in the rabbit.

Nine normal rabbits were placed on the cholesterol-Wesson oil diet for periods of 4 to 11 weeks. Two animals were sacrificed at

four weeks, two at six weeks, two at eight weeks, and three at 11 weeks, and the degree of atherosclerosis determined. Table 4 shows the results obtained from this group of animals. It can be seen that all animals on this diet for six weeks or longer showed severe atherosclerosis (4 to 5 plus) while minimal to moderate (1 to 2 plus) atherosclerosis was present in four weeks. This substantiates the resistance to atherosclerosis of the alloxan-diabetic rabbit as reported by Duff and co-workers. At the end of 11 weeks many of the alloxan-diabetic animals showed only minimal atherosclerosis, while at six weeks all normal animals showed severe atherosclerosis on this diet.

Figure 1 portrays the ultracentrifugal patterns in a normal rabbit, a normal rabbit fed cholesterol, and an alloxan-diabetic rabbit fed cholesterol. The ultracentrifugal photographs of the normal rabbits show the presence of the S_f 3–12 class of molecules and negligible quantities of all other classes of lipoproteins. The photograph of the normal rabbit fed cholesterol portrays the large quantities of all classes of lipotroteins present after two weeks of cholesterol feeding, and with a total serum cholesterol of 1536 mg. per 100 cc. The photographs of the alloxan-diabetic rabbits represent the lipoprotein distribution in animals fed cholesterol for 10 weeks and with final total serum cholesterol levels of 7440 mg. per 100 cc. and 10,120 mg. per 100 cc. The abrupt block in the S_f 100 region with the paucity of molecules below S_f 40, and the huge quantities of lipoproteins above S_f 100 visualize the metabolic defect in this animal. These animals showed only minimal atherosclerosis and maintained the same consistent distribution of lipoproteins throughout the cholesterol feeding regimen.

Summary

1. The alloxan-diabetic rabbit fed cholesterol develops extreme lipemia and hypercholesteremia, and develops a lesser degree of atherosclerosis as contrasted with a normal rabbit fed cholesterol. This is in agreement with the findings previously reported by Duff and co-workers.

2. There is a negative correlation between atherosclerosis and serum cholesterol levels in this group of animals.

3. There is a significant positive correlation between lipoproteins of the S_f 12–30 class and atherosclerosis in these animals, in agreement with other experimental evidence in the rabbit developing atherosclerosis, indicating that this class of molecules correlates well with atherosclerosis.

4. No other class of lipoproteins correlates as well with atherosclerosis as does the S_f 12–30, and, in fact, a significant negative correlation exists between atherosclerosis and lipoproteins of S_f greater than 100.

5. The high correlation between total serum cholesterol and lipoproteins of S_f greater than 100 in the alloxanized rabbit, together with the high proportion of cholesterol transported in this form, provides an explanation of the observed lack of positive correlation between serum cholesterol and atherosclerosis.

6. Molecules above S_f 100 are intensely light scattering and, since they are generally in high concentration in the serum of the alloxanized rabbit fed cholesterol, the extreme turbidity observed is to be anticipated.

7. The alloxan diabetic animal would appear to have a metabolic block in the conversion of lipoproteins of S_f 80–100 and above into lipoproteins of lower S_f classes.

Acknowldegment

The author is extremely grateful to Dr. John W. Gofman and Dr. Hardin B. Jones for their generous assistance and helpful suggestions.

REFERENCES

[1] Gofman, J. W., Lindgren, F. T., Elliott, H. A., Mantz, W., Hewitt, J., Strisower, B., Herring, V., and Lyon, T. P.: The role of lipids and lipoproteins in atherosclerosis. Science **111:** 166, 1950.

[2] —, Jones, H. B., Lindgren, F. T., Lyon, T. P., Elliott, H. A., and Strisower, B.: Blood lipids and human atherosclerosis. Circulation **2:** 161, 1950.

[3] —, Jones, H. B., Gofman, J. W., Lindgren, F. T., Lyon, T. P., Graham, D. M., Strisower, B., and Nichols, A. V.: Lipoproteins in atherosclerosis. Am. J. Med. **11:** 358, 1951.

[4] Duff, G. L., and McMillan, G. C.: The effect of

alloxan diabetes on experimental cholesterol atherosclerosis in the rabbit. I. The inhibition of experimental cholesterol atherosclerosis in alloxan diabetes. II. The effect of alloxan diabetes on the retrogression of experimental cholesterol atherosclerosis. J. Exper. Med. **89:** 611, 1949.

[5] —, AND PAYNE, T. P. B.: The effect of alloxan diabetes on experimental cholesterol atherosclerosis in the rabbit. III. The mechanism of the inhibition of experimental cholesterol atherosclerosis in alloxan-diabetic rabbits. J. Exper. Med. **92:** 299, 1950.

[6] —, AND WILSON, D. C.: Quoted in Duff, G. L., and McMillan, G. C.[5]

[7] PAYNE, T. P. B., AND DUFF, G. L.: Serum lipids and their fractionation in alloxan diabetes in the rabbit. Proc. Soc. Exper. Biol. & Med. **73:** 332 1950.

The Tricardiograph: A Rapid Screening Method for Cardiac Disease

By J. Leonard Brandt, M.D., William Dock, M.D., Robert Landsman, and Charles Passannante, M.E.

To take slit kymograms of the left hemithorax on 6½ by 8½ inch film, a carrier was designed which can be fitted to the arms of a fluoroscope, replacing the screen. On the lateral and cephalad corner, six seconds of galvanometer trace are recorded, the slit kymograph being exposed during the interval from 3.0 to 4.5 seconds. With two galvanometers, the electrocardiogram and ballistocardiogram can be inscribed, thus timing the motions of the heart border, and permitting correlation of ballistic phenomena with ventricular ejection. This device also has promise as a screening method for detecting cardiac disease.

ROUTINE miniature films of the chest in hospitals, public health and industrial surveys have placed the problem of case finding in tuberculosis on a practical, sound and relatively inexpensive basis. The use of this survey method may contribute materially to the gradual decline in the incidence of tuberculosis among the native population of the United States. Minimal and unsuspected tuberculous infections have been detected in time to save many families from the economic disaster and sorrow which would have resulted from tuberculosis becoming clinically manifest.

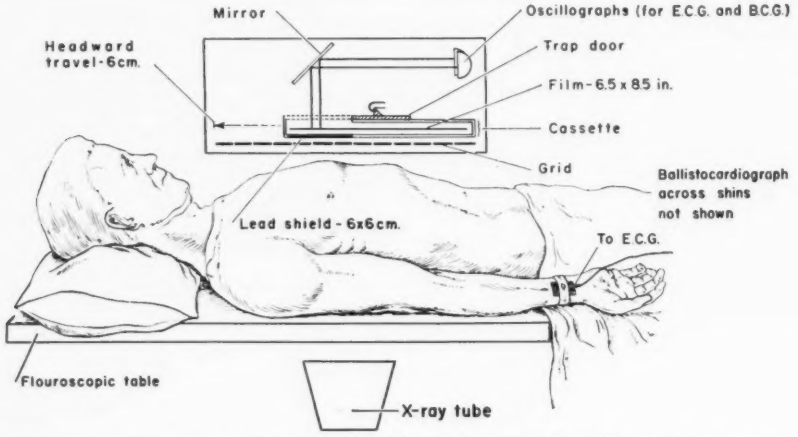

Fig. 1. Diagrammatic representation of the relationships of the tricardiograph for recording left heart border motion, the electrocardiogram, and ballistocardiogram. See text for description.

The need for an equivalent rapid, simple, accurate and inexpensive method for detecting "cardiacs" is obvious. Present day procedures for their detection are expensive and time-consuming, and do not permit simultaneous recording of several important objective aspects of cardiac function.

We have constructed a device which promises to be useful in screening groups of people

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for evidence of heart disease. This records on 6½ by 8½ inch film the slit kymogram of the left heart border for one and one-half seconds, electrocardiogram and ballistocardiogram[1] for six seconds. These films give a permanent record of the contour and motion of the left heart border, the cardiac rhythm and intraventricular conduction, and an index of the vigor of systolic ejection, all in relation to the respiratory cycle. Less than one minute is required for each subject to take his place and complete his film.

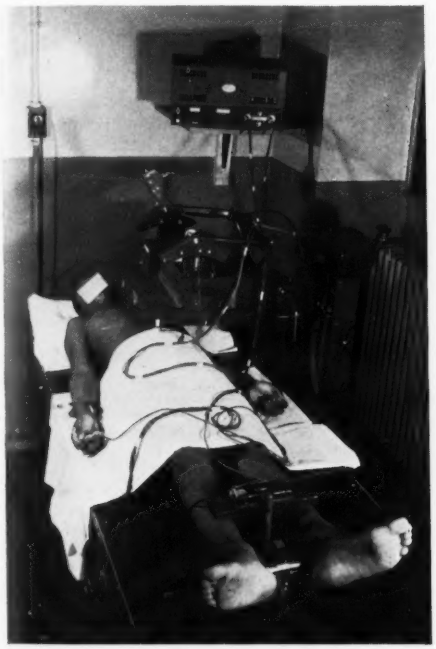

FIG. 2. The tricardiograph in operation. Note the electrocardiograph electrodes on the arms, and the ballistocardiograph across the shins, and the amplifier through which the electrocardiograph and ballistocardiograph are fed. The cassette holder is on the arms of the fluoroscopic screen carrier.

Since this device triangulates on three important aspects of the heart we call it a "tricardiograph." By adding additional channels for recording heart sounds, it may be converted into a true "omnicardiograph."

Figure 1 is a diagrammatic representation of the device. Essentially, it consists of a housing which fits onto the screen arms of a fluoroscope. The housing of the device contains two oscillographs, a lead grid, and a constant speed motor moving a cassette. The cassette is a specially adapted type, the upper left hand corner of which has been replaced by a sliding door to allow 6 by 6 cm. of film to be exposed to the light beams from above, and the corresponding lower surface of the cassette in the left upper corner protected by a lead strip to prevent exposure of the film to the x-rays coming from below.

In operation the patient lies on the fluoroscopic table and the leads for the electrocardiograph and ballistocardiograph are connected to amplifiers which activate the oscillographs. The device is positioned over the subject's left precordial area. (See figure 2.) Pressing a button on the x-ray control box starts the motor and the cassette is driven headward at a speed of 1.0 cm. per second. (See figure 3.) The sliding door of the cassette opens and the light beams of the electrocardiograph and ballistocardiograph inscribe their traces. At the end of three seconds the x-rays are turned on by the cassette carrier and remain on for one and one-half seconds, recording the left heart border, with the electrocardiograph and ballistocardiograph still inscribing. The x-rays go off at the end of four and one-half seconds and an additional one and one-half seconds of electrocardiogram and ballistocardiogram are inscribed, at which time the oscillograph lamp is turned off and the cassette returned to its original position with the sliding door closed. The ballistocardiogram shows the phase of respiration in which the kymograms happened to occur. (See fig. 4.) The entire cycle lasts only about 15 seconds.

DISCUSSION

When Starr and others[2, 3] pointed out that unusual respiratory variation was a striking feature in the ballistocardiogram of patients who subsequently proved to have heart disease, no adequate explanation for the phenomenon was forthcoming. It is known that there is no significant alteration in the peripheral pulses during the respiratory cycle in patients who show a marked respiratory variation.

How these variations in the IJ stroke are related to variations in the excursions of the left heart border is now under study. Our records seem to confirm the theory that the normal IJ is due chiefly to right ventricular ejection, which varies in volume during each cycle of respiration in the same way as the chronously. Such records are not possible with the electrokymograph, since motion of only one or two points along the heart border can be taken at any one time in relation to other phenomena. Such analysis is not necessary to distinguish abnormal from normal tricardiograms.

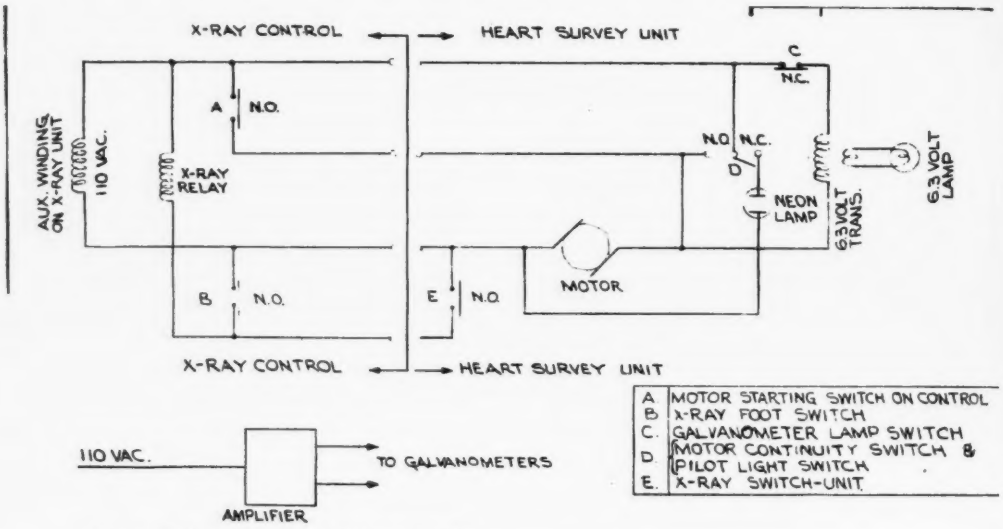

FIG. 3. Wiring diagram for tricardiograph.

When the unit is turned on the 6.3 volt lamp goes on, since its transformer is in series with switch *C*, and a neon lamp (pilot) is also on, since power is fed to it through switch *D*. Switch *A* on the x-ray control is closed, thereby starting the motor and setting the cassette carrier in motion. When the neon lamp goes off, the other side of switch *D* is continuous for the motor, and switch *A* may be released. After 3 cm. (and 3 seconds) of its travel, the carrier actuates the x-ray switch *E* which is in the unit, and holds it closed for one and one-half seconds. The switch *E* actuates the x-ray relay which energizes the x-ray tube. Upon reaching the limit of its headward travel the cassette carrier opens switch *C* and the 6.3 volt lamp is turned off, eliminating the possibility of a reverse trace. The carrier then reverses itself and travels in the opposite direction. Upon reaching the limit of its footward travel the carrier closes switch *C* and opens switch *D*, thereby cutting off power to the motor and stopping the carrier. Simultaneously the oscillograph and pilot lamps are turned on, indicating a completed cycle.

IJ amplitude. The increase in this variation commonly seen in heart disease, including latent coronary disease, is apparently due largely to left ventricular scars or weakness.

It is a relatively simple matter to project the 1.5 cm. frames and trace them upon a conveniently ruled graph paper. This gives an easily interpreted record of the entire left border motion in relation to the electrocardiogram and ballistocardiogram inscribed syn-

It is hoped that this device will prove of aid in elucidating the respiratory variation in the waves inscribed by the ballistocardiogram, and also will provide a useful tool for the rapid screening of a population for latent heart disease.

CONCLUSIONS

1. We have described a device which records a simultaneous electrocardiogram, ballisto-

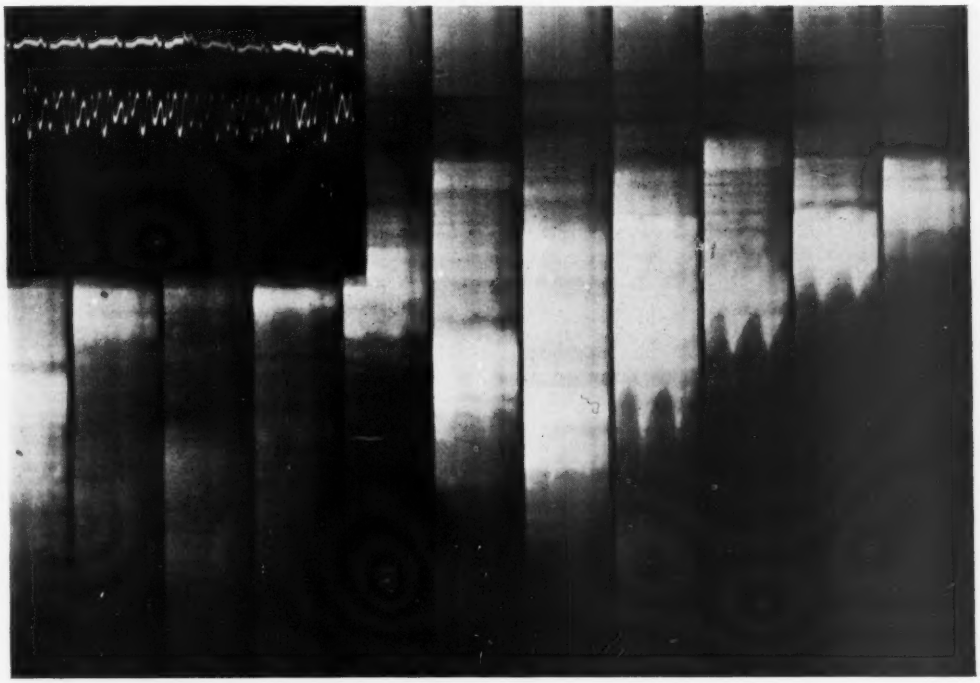

FIG. 4. Tracing of a subject with a palpable impulse in second left intercostal space.

Record shows normal electrocardiogram with large amplitude ballistocardiographic complexes, good left ventricular border motion and a large aortic aneurysm, with minimal pulsation. The slight undulation of the baseline of the ballistocardiogram indicates respiratory cycles.

cardiogram, and slit kymogram of the left heart border on $6\frac{1}{2}$ by $8\frac{1}{2}$ inch film. This device is adaptable to the recording of other cardiac phenomena, and is fitted to the fluoroscope screen arms of a standard fluoroscope.

2. The records are small, permanent and easily filed.

3. Recording requires a minimum of time and effort from both patient and technician.

REFERENCES

[1] DOCK, W., AND TAUBMAN, F.: Some technics for recording the ballistocardiogram directly from the body. Am. J. Med. **7:** 751, 1949.

[2] STARR, I., AND FRIEDLAND, C.: On cause of the respiratory variation of ballistocardiogram with note on sinus arrhythmia. J. Clin. Investigation **25:** 53, 1946.

[3] BROWN, H. R., JR., HOFFMAN, M. J., AND DE LALLA, V., JR.: Ballistocardiographic findings in patients with symptoms of angina pectoris. Circulation **1:** 132, 1950.

The Peripheral Vascular Reactivity of Potassium-Deficient Rats

By RAY H. ROSENMAN, M.D., S. CHARLES FREED, M.D., AND MEYER FRIEDMAN, M.D.

Peripheral vascular reactivity was studied in the potassium-deficient and control rats by measuring the degree of blood pressure response to intravenously injected pressor substances. The pressor response consistently was less in the potassium-deficient rats. The significance of these results with regard to the hypotensive action of potassium deprivation is discussed.

CONSIDERABLE emphasis has been given to the essential role of potassium in the maintenance of the structural and functional integrity of various body tissues. More recently, the present authors[1–3] have obtained evidence that the blood pressure of normal and hypertensive rats maintained upon a potassium-deficient diet is significantly depressed. This depressor response, however, could be prevented by simultaneous deprivation of sodium.[2]

The mechanism by which potassium deprivation induces a lowering of the blood pressure is, as yet, not clarified. Data[2, 3] obtained in this laboratory indicate that the myocardial damage which may follow potassium deficiency probably does not account for the hypotensive response that occurs in either normal or hypertensive rats. An alteration in the peripheral vascular system, however, might well be involved. The following experiments therefore were undertaken in order to test the immediate vascular response to the administration of several pressor substances in rats made potassium deficient.

METHODS

Six to 7 week old male rats (Long-Evans) were divided into three groups which were given the following dietary regimes. The first group of 12 rats (group I) was placed upon a potassium-deficient diet as described,[3] and which was supplemented by an adequate vitamin intake.* A second group of 12 control rats (group II) was placed upon the identical diet except that potassium chloride, 0.5 per cent, was added to the ration. A third group of 12 control rats was fed a stock laboratory diet.

At the end of the ensuing 10 week feeding period the vascular reactivity of each rat was tested by a technic generally similar to that developed by Page and Taylor for dogs[4] and adapted for rats by Masson, Page and Corcoran.[5] Under ether anesthesia the abdomen was opened and a plastic cannula inserted into a branch of the inferior vena cava, providing a method for rapid intravenous injection of the test substances. The animal was then heparinized and a small cannula inserted into the distal aorta and connected to a mercury manometer. After a period of observation during which the blood pressure was allowed to stabilize at a constant level, the following substances were injected intravenously in succession, and the blood pressure changes recorded. Between each injection an adequate time interval was allowed for the return and stabilization of the blood pressure at the basal level. The test substances and their dosage were (a) commercial epinephrine, 0.1 cc. (1 μg.), (b) norepinephrine, 0.1 cc. (1 μg.), (c) angiotonin,† 0.2 cc. (5 mg. containing 2 units), and (d) renin,† 0.1 cc. (0.5 mg.). It is recognized that errors inherent in the instruments and technic employed in obtaining the blood pressures as well as the surgical trauma to which the animals were exposed prevent any conclusions from being drawn with regard to the initial pressures that were observed. Nevertheless, the method is believed reliable with regard to changes in pressure which occurred in response to injection of the pressor substances.

From the Mount Zion Hospital, the Harold Brunn Institute for Cardiovascular Research, San Francisco, Calif.

This work was done during the tenure of a Research Fellowship of the American Heart Association held by R. H. R.

Aided by a grant from the U. S. Public Health Service.

* We are indebted to Hoffmann-LaRoche, Inc., for generous supplies of Litrison, used to provide the supplements added to the synthetic diets.

† We are grateful to Dr. Arthur C. Corcoran and Dr. Kenneth Savard of the Cleveland Clinic Foundation for generous supplies of angiotonin and renin furnished for these studies.

Results

The rats that had been maintained upon the stock diet and upon the synthetic control diet showed comparable pressor responses to the test substances. Furthermore, the synthetic control diet was shown to be adequate since growth and weight gain in these rats were similar to growth and weight gain in rats fed the stock diet. Therefore, for simplicity, only the results obtained in the rats fed the synthetic diets will be presented.

Table 1 presents the blood pressure changes which followed the intravenous injection of the test substances and the figure depicts the average blood pressure responses which were observed. The average and range of values obtained in the potassium-deficient rats (group I) were in marked contrast to the control animals (group II). Thus, the pressor response to all of the test substances was consistently diminished in the potassium-deficient animals (see fig. 1). There was some variation in the magnitude of this decreased response to the various test substances. The blood pressure rise after epinephrine injection in the potassium-deficient rats was about one-half as great as in the control animals, while the injection of angiotonin and renin induced less than one-half, and norepinephrine only one-third of the normal pressor response.

TABLE 1.—*Changes in Blood Pressure following Intravenous Injection of Pressor Substances into Potassium-Deficient Rats*

Type of Rat	No of Rats	Weight (Gm.)	Average Blood Pressure Responses After Intravenous Injection of Pressor Substances (mm. Hg)											
			Epinephrine			Norepinephrine			Angiotonin			Renin		
			Initial	Peak	Increase	Initial	Peak	Increase	Initial	Peak	Increase	Initial	Peak	Increase
Potassium-Deficient	12	180 (125–233)	74 (33–96)* S.E.M.† ±4.0	98 (53–118) ±4.7	±24 (4–44) ±3.0	81 (51–100) ±3.9	92 (63–130) ±4.5	+11 (4–30) ±2.0	78 (59–98) ±3.1	111 (85–136) ±3.9	+33 (22–50) ±3.1	84 (72–96) ±2.5	97 (84–112) ±3.6	+13 (6–25) ±1.9
Control	12	324 (290–366)	79 (60–100) ±4.1	120 (110–137) ±3.3	+41 (36–53) ±2.1	81 (58–100) ±3.7	112 (96–138) ±4.1	+31 (22–38) ±1.7	82 (54–106) ±5.2	149 (114–180) ±6.1	+67 (48–90) ±3.5	96 (74–114) ±4.1	133 (114–176) ±6.3	+37 (20–62 ±3.2

* Figures in parentheses refer to range of values obtained.
† Standard error of the mean.

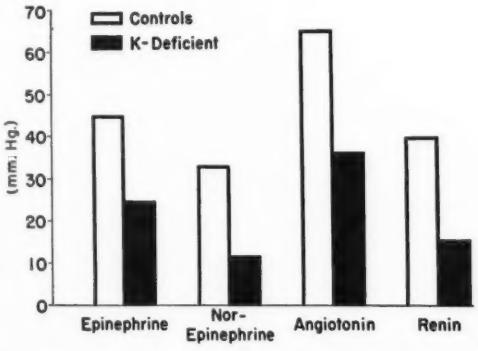

FIG. 1. Average blood pressure response to intravenous injection of pressor substances into potassium-deficient rats.

Discussion

It has been shown recently that the motility and muscular tone of the gastrointestinal tract and urinary bladder were progressively decreased in potassium-deficient rats.[6, 7] These results suggested that the smooth muscle of the peripheral vascular system and, in particular, of the arterioles similarly might become atonic during potassium deprivation. The evidence obtained in these experiments lends strong support to this supposition. The consistently decreased response to the various pressor agents that was observed in the potassium-deficient rats, in contrast to that in the control animals, strongly suggests that potassium deprivation induces a decreased arteriolar tone. Although a part of its pressor action is central in the case of epinephrine, renin and angiotonin act largely by peripheral vasoconstriction.[8, 9] The markedly diminished response to norepinephrine is particularly significant since it has been well

shown that this substance exerts a pressor action solely by its peripheral effects, inducing arteriolar vasoconstriction, but without increasing the cardiac output.[10] This evidence suggests that the mechanism of the decreased responsiveness of the potassium-deficient rat to pressor agents is localized to the periphery of the arterial system.

These results also suggest that the depressor effect of prolonged potassium deprivation in both normotensive[1, 2] and hypertensive[3] rats is at least partly related to a reduction of peripheral vascular resistance, effected by a decreased arteriolar tone. That such a decrease in peripheral resistance actually is the cause of the hypotension which follows chronic potassium deprivation, remains, however, to be demonstrated.

Although the mechanism of decreased vascular reactivity occurring in prolonged potassium deprivation would appear to be related to a decreased arteriolar muscular tone, it must be considered that both sodium and potassium are intimately connected with the transmission of nerve impulses.[11, 12] It is also well known that potassium is closely related to the acetylcholine metabolism at the nerve endings.[11] Potassium deprivation, by itself, or acting through a disturbed sodium-potassium ratio, may thus alter the arteriolar nerve-muscle system and be a factor in the induction of hypotension.

Summary

Peripheral vascular reactivity has been studied in potassium-deficient and in control rats. The vascular reactivity was measured by the degree of response to intravenously injected epinephrine, norepinephrine, angiotonin, and renin.

The pressor response to all of the test substances was consistently and significantly less in the potassium-deficient rats, compared with the results obtained in the control animals.

It is suggested that a decreased peripheral vascular resistance may account, in part, for the hypotensive action of potassium deprivation in both normotensive and hypertensive rats.

REFERENCES

[1] Freed, S. C., and Friedman, M.: Hypotension in the rat following limitation of potassium intake. (Preliminary report). Science **112:** 788, 1950.

[2] —, and —: The depressor effect of potassium restriction on the blood pressure of the rat. Proc. Soc. Exper. Biol. & Med. **78:** 74, 1951.

[3] Friedman, M., Rosenman, R. H., and Freed, S. C.: The depressor effect of potassium deprivation on the blood pressure of the hypertensive rat. Am. J. Physiol. **167:** 457, 1951.

[4] Page, I. H., and Taylor, R. D.: Variations of vascular reactivity in normal and hypertensive dogs. Am. J. Physiol. **156:** 412, 1949.

[5] Masson, G. M. C., Page, I. H., and Corcoran, A. C.: Vascular reactivity of rats and dogs treated with desoxycorticosterone acetate. Proc. Soc. Exper. Biol. & Med. **73:** 434, 1950.

[6] Webster, D. R., Henrikson, H. W., and Currie, D. J.: The effect of potassium deficiency on intestinal motility and gastric secretion. Ann. Surg. **132:** 779, 1950.

[7] Henrikson, H. W.: Effect of potassium deficiency on gastrointestinal motility in rats. Am. J. Physiol. **164:** 263, 1951.

[8] Page, I. H.: On the nature of the pressor action of renin. J. Exper. Med. **70:** 521, 1939.

[9] Page, I. H., and Helmer, O. M.: A crystalline pressor substance (angiotonin) resulting from the reaction between renin and renin-activator. J. Exper. Med. **71:** 29, 1940.

[10] Goldenberg, M., Pinez, K. L., Baldwin, E. de F., Greene, D. G., and Roh, C. E.: The hemodynamic response of man to nor-epinephrine and epinephrine and its relation to the problem of hypertension. Am. J. Med. **5:** 792, 1948.

[11] Gass, H., Cherkasky, M., and Savitsky, N.: Potassium and periodic paralysis: metabolic study and physiological considerations. Medicine **27:** 105, 1948.

[12] Hunt, C. C., and Kuffler, S. W.: Pharmacology of the neuromuscular junction. Pharmacol. Rev. **98:** 96, 1950.

Effect of Potassium Administration on (1) Peripheral Vascular Reactivity and (2) Blood Pressure of the Potassium-Deficient Rat

By Meyer Friedman, M.D., S. Charles Freed, M.D., and Ray H. Rosenman, M.D.

One hour after administration of potassium chloride to potassium-deficient rats, the depressed peripheral vascular response to pressor substances was significantly elevated. Administration of potassium chloride to potassium-deficient rats also returned to higher levels the lowered blood pressure of previously normotensive, as well as hypertensive rats. It appears that the depressor effect of potassium deprivation is due to the loss of peripheral vascular reactivity, both of which are rapidly restored by potassium administration specifically.

PREVIOUS studies from our laboratory have shown that potassium deprivation has a significant depressor effect in the normotensive[1, 2] and a profound effect in the hypertensive rat.[3] Although various lesions usually were found in both the heart and kidneys of these animals, we were not able to find any correlation between their severity and the degree of hypotension observed. Finally, it was found[4] that these same rats exhibited a marked decrease in their peripheral vascular reactivity as judged by their pressor response to the predominantly peripherally acting substances, norepinephrine, angiotonin and renin. This last, of course, suggested that the depressor response observed in the potassium-deficient rat was not due to some structural defect in the heart or kidney but to a functional one in the peripheral arteriole, occasioned by potassium deficit.

If this latter concept were correct, then administration of potassium to a rat previously deprived of potassium should result in (1) an increase in peripheral vascular reactivity, and (2) an increase in the blood pressure occurring *pari passu* with the former. The present report, detailing the effects of potassium administration on the peripheral vascular reactivity and blood pressure of the potassium-deficient rat indicate that the above concept is probably correct.

Part I

Effect of Potassium Replacement on Peripheral Vascular Reactivity

Methods

Twenty-one Long-Evans rats (6 weeks old) were deprived of adequate potassium for 10 weeks by the ingestion of a diet containing 0.006 per cent potassium and 0.38 per cent sodium.[3] A control group of 14 rats was given the same diet except that its potassium content was 0.4 per cent.

The effect of potassium upon the peripheral vascular reactivity of the group of 21 potassium-deficient rats was determined by a modification of the technic developed by Page and Taylor for dogs[5] and adapted for study of vascular reactivity in the rat by Masson, Page, and Corcoran.[6] First, the pressor responses of 9 of the 21 rats were observed after the intravenous injection of norepinephrine, angiotonin, and renin, according to previously described methods.[4] Similar studies were done on 6 of the 14 control rats. Then, the same vasoconstrictor drugs* were tested in the remaining potassium-deficient and control rats after they had received a subcutaneous injection of 10 cc. of isotonic potassium chloride solution (155 mEq. per liter) one hour before.

From the Mount Zion Hospital, the Harold Brunn Institute for Cardiovascular Research, San Francisco, Calif.

This work was done during the tenure of a Research Fellowship of the American Heart Association held by R. H. R.

Aided by a grant from the U. S. Public Health Service.

* We wish to express our appreciation to Dr. Arthur C. Corcoran and Dr. Kenneth Savard of the Cleveland Clinic for the generous supplies of angiotonin and renin which they placed at our disposal for these studies.

Results

The pressor responses which occurred are presented in table 1 and the average responses are depicted in figure 1. It can readily be seen that the administration of potassium to the rat previously deprived of it consistently increased his mean pressor response to each of the three substances administered. Thus, the average pressor response of the deficient rat to each of the test substances was approximately doubled. On the other hand (see fig. 1), no significant increase in pressor response was noted in the control animals after similar potassium injection.

TABLE 1. *Changes in Mean Blood Pressure following Intravenous Injection of Pressor Substances into Potassium-Deficient Rats before and after the Administration of Potassium*

Type of Rat	No. of Rats	Average Blood Pressure Responses After Intravenous Injection of Pressor Substances (mm.Hg)								
		Norepinephrine			Angiotonin			Renin		
		Initial	Peak	Increase	Initial	Peak	Increase	Initial	Peak	Increase
Potassium-deficient	9	76	84	+8	73	98	+25	72	89	+17
		(40–100)*	(62–108)	(2–16)	(40–100)	(82–120)	(10–56)	(56–96)	(72–110)	(10–24)
		S.E.M.† ±5.9	±4.8	±1.4	±6.2	±4.6	±4.8	±4.7	±4.2	±1.2
Potassium-deficient: 1 hour after administration of potassium‡	12	85	102	+17	88	140	+52	91	119	+28
		(40–104)	(54–128)	(10–26)	(46–104)	(72–168)	(26–74)	(80–110)	(104–170)	(14–70)
		±5.5	±6.2	±1.6	±5.1	±8.3	±4.7	±4.9	±7.4	±5.2
Control	8	68	90	+22	73	141	+68	83	129	+46
		(52–84)	(72–104)	(16–26)	(50–90)	(94–162)	(44–90)	(56–102)	(88–144)	(30–68)
		±3.9	±3.5	±1.0	±5.2	±9.9	±5.4	±6.2	±7.0	±5.0
Control: 1 hour after administration of potassium‡	6	78	104	+26	83	149	+66	82	127	+45
		(44–100)	(60–124)	(16–36)	(44–106)	(92–190)	(46–80)	(44–108)	(62–176)	(18–70)
		±7.5	±8.7	±3.0	±8.4	±12.0	±4.9	±8.9	±16.0	±7.7

* Figures in parentheses refer to range of values obtained.

† Standard error of the mean.

‡ 10 ml. isotonic potassium chloride injected subcutaneously one hour before beginning of experiment.

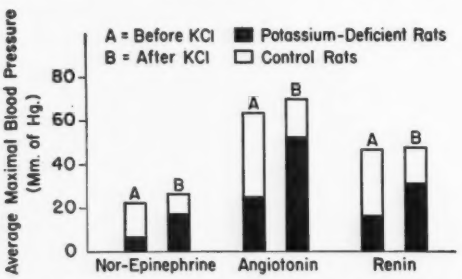

FIG. 1. The average pressor response of potassium-deficient rats before and one hour after subcutaneous injection of potassium chloride.

PART II

EFFECT OF POTASSIUM REPLACEMENT ON BLOOD PRESSURE

Methods

The preceding observations indicated that parenteral administration of potassium rapidly improved the peripheral vascular deficiency occurring in the potassium-deficient rat. Moreover, the rapidity of recovery strongly indicated that the defect itself was not only reversible but probably functional in nature.

In order to determine whether potassium replacement also would restore the lowered blood pressure of deficient rats to the normotensive level existing before the deprivation of this cation, 10 initially normotensive rats were deprived of dietary potassium for 10 weeks. A control group of 10 rats was maintained on the same diet but also containing adequate potassium (0.4 per cent). After this preliminary period, the deficient and control rats were given a subcutaneous injection of 10 cc. of isotonic potassium chloride (155 mEq. per liter), and later potassium chloride solution (1 per cent) in lieu of drinking water. Blood pressures were taken on these rats before and 1 and 24 hours after the subcutaneous administration of potassium, by means of the microphonic manometer.[7] Food was withheld from all rats during this 24 hour interval.

In order to determine whether potassium replacement would restore the blood pressure of a group of deficient rats, previously hypertensive (that is, before

the dietary restriction of potassium), the following experiment was done. Five hypertensive rats[8] were placed on the potassium-deficient diet (0.006 per cent potassium). At the end of eight weeks, these five rats exhibited a marked decrease in systolic blood pressures, compared with the control hypertensive rats. They were then fed the identical diet except that the potassium content was increased (0.4 per cent potassium) and their blood pressures, together with those of the original controls, were followed weekly. The control rats were fed the latter diet (0.4 per cent potassium) throughout the experiment.

Results

A. Upon Previously Normotensive Rats. The average systolic blood pressure of the 10 rats given the potassium-deficient diet for 10 weeks was 82 mm. Hg (range: 56 to 100 mm. Hg; S.E. mean: ±2.9). These findings confirmed our earlier observations of the hypotensive effect of potassium restriction.[1, 2] As figure 2 depicts, parenteral, and later oral, administration of potassium to 10 of these rats was followed by a marked rise in their pressure as early as 60 minutes after the injection. At this time the average systolic pressure had risen to 102 mm. Hg (range: 56 to 120; S.E. mean: ±6.4). Moreover, 24 hours after the initial injection of potassium the average pressure of these rats had reached 111 mm. Hg (range: 96–122; S.E. mean: ±2.6), a rise of 29 mm. in a single day. Administration of the same amount of potassium to the control normotensive rats had no significant effect. (See fig. 2.) In the latter, the average initial pressure of 125 mm. Hg (range: 100 to 140; S.E. mean: ±5.3) decreased to 118 mm. Hg (range: 96 to 144; S.E. mean: ±4.7), and 24 hours after injection of potassium, the average pressure was 112 mm. Hg (range: 80 to 144; S.E. mean: ±5.8).

B. Upon Previously Hypertensive Rats. Replacement of potassium in previously hypertensive but now normotensive potassium-deficient rats was found to lead to a return of the hypertension (see fig. 3). Thus, the average blood pressure of the five hypertensive rats fell to 136 mm. Hg (range: 122 to 160; S.E. mean: ±7.0) after eight weeks of potassium deprivation, in contrast to the average pressure of 188 mm. Hg (range: 146 to 240; S.E. mean: ±10.3) observed in the controls. However, when the deficient rats were again fed the same diet but with adequate potassium, a rise in pressure was noted within a week. As figure 3 illustrates, this rise continued until the animals once again became significantly hypertensive, the average systolic pressure rising to 180 mm. Hg (range: 120 to 230; S.E. mean: ±19.6) at the eighth week. In the control group, the average pressure increased slightly during this interval to 194 mm. Hg (range: 142 to 240; S.E. mean: ±23.2).

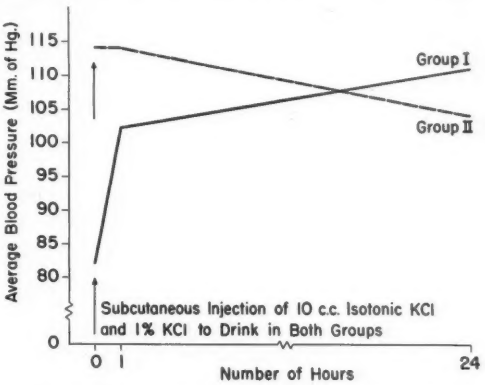

FIG. 2. The effect of potassium replacement on the blood pressure of normotensive rats previously fed a potassium-deficient diet. *Group I*, potassium-deficient rats injected with potassium chloride. *Group II*, control rats injected with potassium chloride.

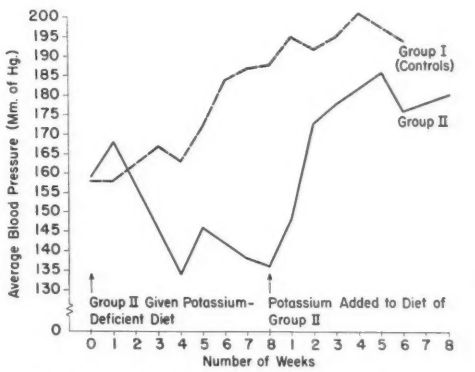

FIG. 3. The effect of potassium replacement on the blood pressure of hypertensive rats previously fed a potassium-deficient diet.

DISCUSSION

In a previous study[4] it was found that the reactivity of the peripheral vasculature was depressed markedly by potassium deprivation. The restoration of this peripheral vascular re-

activity (as measured by the pressor response of the animal to vasoconstrictor substances) in potassium-deficient rats, after administration of potassium, strongly suggests that the original decrease in reactivity was due to a specific deficiency of this same cation. In view of the fact that a generalized decrease in the tone of smooth muscle of the gastrointestinal and genitourinary systems has been found in the potassium-deficient animals,[9, 10] it seems possible that the peripheral vascular defect herein noted may well be due to a decrease in the tone of arteriolar musculature.

The present results also indicate that the fall in blood pressure occurring in both the normotensive and hypertensive rat subjected to potassium deprivation can be quickly reversed by the administration of potassium. This increase in pressure after potassium administration moreover, appears to take place, *pari passu*, with the return of peripheral vascular reactivity. This rapid and concomitant rate of return of both reactivity and blood pressure after administration of potassium not only suggests that both the decrease in reactivity and pressure are specifically due to the absence of this cation, but also that the two processes are causally related. In other words, the changes of blood pressure noted in the rat after potassium deprivation appear to be due to the changes produced by the latter in the peripheral vasculature, changes which are functional in nature and quickly reversible after administration of potassium alone.

Summary

Administration of potassium was found to effect a rapid restoration of the decreased peripheral vascular reactivity found in the potassium-deficient rat. Administration of the same cation also was observed to restore the blood pressure of previously normotensive and hypertensive rats to the levels present before deficiency of potassium had been accomplished. The relationship of the decrease in the peripheral vascular reactivity and the blood pressure in the potassium-deficient rat was discussed.

REFERENCES

[1] Freed, S. C., and Friedman, M.: Hypotension in the rat following limitation of potassium intake. Science **112:** 788, 1950.

[2] —, and —: The depressor effect of potassium restriction on the blood pressure of the rat. Proc. Soc. Exper. Biol. & Med. **78:** 74, 1951.

[3] Friedman, M., Rosenman, R. H., and Freed, S. C.: The depressor effect of potassium deprivation on the blood pressure of hypertensive rats. Am. J. Physiol. **67:** 475, 1951.

[4] Rosenman, R. H., Freed, S. C., and Friedman, M.: The peripheral vascular reactivity of potassium-deficient rats. Circulation. This issue.

[5] Page, I. H., and Taylor, R. D.: Variations of vascular reactivity in normal and hypertensive dogs. Am. J. Physiol. **156:** 412, 1949.

[6] Masson, G. M. C., Page, I. H., and Corcoran, A. C.: Vascular reactivity of rats and dogs treated with desoxycorticosterone acetate. Proc. Soc. Exper. Biol. & Med. **73:** 434, 1950.

[7] Friedman, M., and Freed, S. C.: Microphonic manometer for indirect determination of systolic blood pressure in the rat. Proc. Soc. Exper. Biol. & Med. **70:** 670, 1949.

[8] Grollman, A.: A simplified procedure for inducing chronic renal hypertension in the mammal. Proc. Soc. Exper. Biol. & Med. **57:** 102, 1944.

[9] Webster, D. F., Henrikson, H. W., and Currie, D. J.: The effect of potassium deficiency on intestinal motility and gastric secretion. Ann. Surg. **132:** 779, 1950.

[10] Henrikson, H. W.: Effect of potassium deficiency on gastrointestinal motility in rats. Am. J. Physiol. **164:** 263, 1951.

Hepatic Circulation in Cirrhosis of the Liver

By S. E. Bradley, M.D., F. J. Ingelfinger, M.D., and G. P. Bradley, M.D.

The hepatic blood flow (EHBF) was estimated by the bromsulfalein method in 39 cirrhotic patients. In 91 normal subjects hepatic blood flow averaged 1530 ml. per minute, and in the cirrhotics, hepatic blood flow averaged 1090 ml. per minute. In association with this highly significant reduction in blood flow, hepatic arteriovenous oxygen difference increased and bromsulfalein extraction fell. These findings indicate that hepatic blood flow tends to decrease more than oxidative metabolism of residual functional cells, so that relative ischemia and hypoxia of active liver tissue develop in cirrhotic disease.

THE HEPATIC vasculature is strikingly transformed by the structural changes that occur in cirrhotic disease. The destruction of parenchymal tissue, reparative hyperplasia of liver cells, and overgrowth of fibrous tissue bring about an attenuation of blood vessels and a reduction in the complexity of the vascular network.[1-3] This process appears to affect preponderantly the branches of the portal vein. Thus, portal venous hypertension and the development of collateral venous drainage may be attributed to the structural obstruction in the liver to the inflow of portal venous blood. It has been claimed that hepatic arterial inflow may actually increase in this situation and that total hepatic blood flow may be augmented in cirrhotic disease. This view has found support in studies by Herrick[4] and Dock[5] of the postmortem perfusibility of the hepatic circuit in the cirrhotic liver. There is little anatomic evidence, however, of diminished resistance to arterial inflow, and it seems probable that any structural change that affects the hepatic vasculature at the level of the sinusoids would affect both arterial and venous perfusion. The development of venous catheterization technics by Cournand and his associates[6] has provided a direct means of examining the behavior of the hepatic circulation in patients with cirrhosis of the liver.

Methods

The hepatic blood flow has been estimated by the bromsulfalein (BSP) clearance technic in 39 patients with cirrhotic disease. In 29 subjects a diagnosis of Laennec's cirrhosis (17 had a history of chronic alcoholism and 12 did not) was made on the basis of prolonged clinical study. Measurements were also made in patients with cirrhosis due to schistosomiasis (four), syphilis (one) and chronic periportal inflammation (biliary cirrhosis, one). Four subjects with Banti's syndrome due to extrahepatic portal venous obstruction are included in this series. Determination of hepatic oxygen extraction was made in 29 of these subjects and in 12 additional persons with cirrhosis (seven with a history of chronic alcoholism and four without) and extrahepatic block (one). The diagnosis was confirmed by biopsy or at necropsy in 46 of the 51 individuals comprising the total series. None of these individuals was jaundiced or in frank cholemia, but all presented clear-cut evidence of portal venous hypertension. Hepatic blood flow was also estimated in 91 "normal" subjects and hepatic oxygen extraction was measured in 27. Data obtained in studies of 14 cirrhotic subjects and of 25 normal individuals included in this paper have been reported previously in preliminary form.[7, 8]

All subjects were selected from patients on the wards of the Presbyterian Hospital in New York City and the Evans Memorial Hospital in Boston, and were studied under comparable conditions of quiet recumbency in the fasting state. An infusion of bromsulfalein (from 200 to 400 mg. per 100 ml. in isotonic saline or glucose) was administered intravenously at a constant rate of about 4 ml. per minute, after a "priming" dose of 150 mg. had been given. A calibrated Murphy drip and tunnel clamp or a Bowman pump* was used to maintain the rate of infusion as nearly constant as possible. An extra length plastic ureteral catheter was inserted into a medial antecubital vein and passed under fluoroscopic control by way of the superior vena cava, right atrium and inferior vena cava into a right hepatic vein. A glucose infusion containing a small amount of heparin (2 mg. per 100 ml. of infusion) was allowed to flow slowly through the venous

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* Obtained from Process and Instruments Company, Brooklyn, New York.

catheter throughout the procedure. After an appropriate period (about 30 minutes) to permit equilibration of the bromsulfalein concentration in the blood, peripheral venous or arterial blood was sampled and from 5 to 10 minutes thereafter a sample of hepatic venous blood was taken through the catheter after withdrawing 2 or 3 ml. of blood and discarding it in order to avoid admixture of the blood sample with heparin-infusion solution. This procedure was repeated at least two or three times at 10 minute intervals. Whenever possible, arterial and hepatic venous blood was sampled simultaneously under anaerobic conditions in order to determine hepatic oxygen uptake. Bromsulfalein was determined colorimetrically in serum or heparinized plasma using a calibration curve based on bromsulfalein standards made up in plasma half diluted with isotonic saline. A Coleman Jr. colorimeter was used in the vast majority of these studies and readings were made at 580 λ using each plasma or serum sample as its own blank. A reading was made after adding a few drops of 20 per cent potassium hydroxide to the sample. Transmittance curves indicated maximal absorption between 570 and 580 λ when standards were made up in isotonic saline or pooled plasma. Some apparent loss of bromsulfalein occurred when plasma was allowed to stand owing to change in plasma pH toward alkalinity. At high concentrations of bromsulfalein isotonic saline solution was used to dilute the plasma sample in order to avoid clouding or precipitation of protein. Hemolyzed samples could not be used because of a variable and uncontrolled degree of clearing with alkalinization. High concentrations of bilirubin also made accurate determination of bromsulfalein impossible. Oxygen content and capacity of the blood were determined by the method of Van Slyke and Neill.[9] The oxygen concentrations were corrected, when necessary, for inadvertant dilution, on the basis of average arterial oxygen capacities.

The hepatic blood flow (EHBF) was estimated from the hepatic bromsulfalein removal rate and hepatic bromsulfalein arteriovenous difference.[7] Bromsulfalein removal was calculated from the rate of infusion and the rate of change in total plasma content of bromsulfalein, assuming distribution of the protein-bound dye in the plasma alone and calculating plasma volume on the basis of body surface. In general the plasma level remained relatively constant (see tables). An effort was made to keep the plasma concentration below 2 mg. per 100 ml., since saturation of hepatic removal mechanisms occurs at higher levels and bromsulfalein extraction (hepatic bromsulfalein arteriovenous difference divided by arterial bromsulfalein concentration) tends to fall. When bromsulfalein extraction was less than 10 per cent at peripheral arterial or venous concentrations greater than 1 mg. per 100 ml. or less than 15 per cent at values less than 1 mg. per 100 ml., the determinations were considered valueless and discarded because the hepatic arteriovenous difference was too small under these circumstances for accurate measurement.

Validity of the Method for Estimating Hepatic Blood Flow

The method used in this study for estimating hepatic blood flow is based on three major assumptions: (1) that blood obtained from a right hepatic vein is representative of the mixed venous blood draining from the liver as a whole; (2) that the concentration of bromsulfalein in the peripheral arterial or venous blood is equal to the concentration in blood entering the liver; and (3) that bromsulfalein is removed from the blood exclusively by the liver. The situation obtaining in the splanchnic vasculature as a result of portal cirrhosis makes it necessary to examine these points in some detail.

Exploratory sampling of blood from various sites in any single liver has been carried out in eight subjects, two of whom had cirrhosis of the liver.[10] Bromsulfalein extraction differed at the extremes by 26, 20, 14, 13, 10 and 9 per cent in the normal individuals, and by 2 per cent in each of the cirrhotics. These results indicate relatively uniform removal of the dye throughout every part of the hepatic parenchyma. The contribution of nonextractive tissues, such as the capsule, may account for a tendency to reduced extraction in areas close to the periphery of the liver. Samples obtained close to the inferior vena cava also tended to show somewhat lower extraction of bromsulfalein, possibly because regurgitation of blood resulted in contamination of the hepatic venous sample with blood containing a higher concentration of the dye. In view of these observations every effort was made to maintain the position of the tip of the catheter deep in the center of the right hepatic lobe. Since the hepatic veins drain separately into the inferior vena cava it is impossible to sample mixed hepatic venous blood. Hence any inequality of extraction by different parts of the liver cannot be corrected and error is introduced into the measurement of flow. For this reason chiefly the value obtained is referred to as the "estimated hepatic blood flow" (EHBF).

TABLE 1.—*Estimated Hepatic Blood Flow in "Normal" Human Subjects*

Subjects	Sex	Age yrs.	Surface area	P_{BSP}	E_{BSP}	R_{BSP}	Hematocrit	EHBF
			M.²	*mg.%*	%	*mg./min.*	%	*ml./min.*
A. C.	M	24	1.76	1.83	58.0	5.5	46.0	970
A. P.	F	24	1.65	2.00	53.0	5.4	49.0	1000
F. R.	F	24	1.37	1.43	53.0	4.4	46.0	1060
J. M.	M	25	1.99	1.20	86.0	6.2	45.0	1090
J. Mc.	M	22	1.75	1.52	59.5	5.5	44.5	1090
J. F.	M	28	2.07	2.35	48.0	6.0	51.0	1090
C. M.	M	33	1.90	1.33	72.0	5.7	46.0	1110
R. Mc.	M	37	1.82	1.64	59.5	5.7	48.0	1120
M. H.	F	22	1.40	1.60	37.5	4.3	37.5	1130
E. M.	F	55	1.88	1.52	37.0	3.9	40.0	1140
R. S.	F	20	1.58	1.30	59.0	4.6	48.0	1150
W. S.*	M	51	2.02	1.30	64.0	5.4	44.0	1160
S. J.	M	28	1.60	1.20	48.5	4.3	37.0	1170
P. W.	F	36	1.49	0.90	54.5	3.9	33.0	1190
J. F.	M	23	1.77	1.67	44.0	5.7	36.0	1190
G. H.	M	23	1.69	1.16	73.5	5.2	49.0	1200
A. A.	M	36	1.91	1.29	73.0	5.8	48.5	1200
F. G.	M	21	1.73	0.75	88.0	4.1	49.0	1220
K. Mc.	F	46	1.32	0.70	70.5	4.0	37.0	1240
M. R.	F	26	1.46	1.14	51.0	4.0	45.0	1250
N. P.*	M	60	1.70	1.04	71.0	4.9	48.0	1260
W. R.*	M	33	1.91	1.24	72.0	6.0	47.0	1270
J. S.	M	51	1.78	1.50	50.5	5.0	48.0	1280
H. O.	M	32	1.92	0.95	78.5	5.5	42.5	1280
M. S.	F	40	1.61	0.70	84.5	4.2	45.0	1290
R. V.*	M	37	2.05	1.36	67.5	6.2	48.0	1290
N. O.	F	35	1.60	1.25	49.5	4.6	41.5	1290
D. D.	M	21	1.71	1.45	52.0	5.4	44.5	1300
E. C.	F	27	1.65	1.46	47.5	5.2	43.0	1310
V. B.	F	19	1.53	1.48	46.0	4.9	45.0	1310
C. T.	M	21	1.93	1.22	82.0	6.5	51.0	1320
J. S.	M	23	1.61	0.87	71.0	4.2	48.5	1320
D. C.	M	30	1.50	0.75	75.5	4.9	30.0	1340
C. M.	M	57	1.50	1.13	83.5	7.3	43.0	1350
A. D.*	M	54	1.82	0.92	65.5	4.5	44.0	1350
A. D.	M	20	1.85	1.21	65.0	6.0	42.0	1360
A. B.	F	33	1.61	0.65	91.5	4.7	42.0	1370
D. D.	M	56	1.60	0.90	43.5	3.4	39.0	1450
V. P.	M	27	1.77	1.12	68.0	5.6	49.5	1450
H. T.	M	22	1.81	0.80	81.5	5.2	45.0	1450
L. W.	F	20	1.62	0.97	60.0	5.5	35.0	1480
A. B.	M	41	1.68	1.28	41.0	4.3	45.0	1500
M. T.	M	36	1.55	0.50	88.0	4.1	38.0	1500
M. H.*	M	24	2.06	0.72	87.0	5.4	43.5	1530
J. T.	M	31	1.90	1.42	44.0	5.4	44.0	1530
R. P.	M	20	1.90	0.87	70.0	5.1	45.0	1530
A. S.	M	28	1.78	1.62	37.0	5.6	40.0	1540
P. Mc.*	M	43	1.75	1.34	45.0	5.3	43.0	1540
E. G.	M	51	1.71	1.00	47.0	4.4	40.0	1550
M. B.	M	21	1.68	0.77	72.0	5.0	44.0	1550
W. H.*	F	63	1.54	0.60	66.5	4.0	36.0	1560
J. D.	M	49	1.75	1.47	35.0	4.1	50.0	1590
J. T.	M	29	2.09	1.10	70.5	6.3	49.0	1600
J. W.*	M	48	1.73	0.85	61.5	4.4	48.5	1620
R. B.	M	47	1.90	1.00	45.0	4.9	34.0	1630
L. C.	M	22	1.78	0.65	84.0	5.3	40.0	1630
A. E.	M	39	1.70	0.94	56.5	5.4	38.5	1640
W. T.	M	39	1.85	0.85	64.0	4.8	43.0	1650
S. D.	M	33	1.94	1.05	47.0	3.9	52.5	1660
K. H.	M	52	1.76	0.74	60.0	5.1	31.5	1670
C. H.	M	29	1.74	1.08	47.0	4.8	44.0	1670
F. B.	M	26	1.70	0.85	54.0	4.0	48.5	1680
M. B.	F	40	1.33	1.22	34.0	4.1	41.5	1700
R. C.	M	21	1.85	1.02	57.0	5.3	46.5	1720
J. B.	M	47	1.99	0.72	65.0	4.3	48.0	1730
L. S.	M	50	1.70	2.04	27.0	5.1	47.0	1730
A. S.	M	24	1.86	0.60	75.0	4.3	44.0	1730
J. A.	F	24	1.75	1.08	52.0	5.6	44.0	1770
E. W.	F	33	1.65	0.84	41.0	4.1	34.5	1790
J. S.	M	25	1.98	1.35	49.5	6.3	47.0	1790
J. P.	M	37	1.60	0.72	54.0	4.1	41.5	1810
F. C.	M	21	1.94	0.73	91.0	5.6	53.5	1810
L. K.	M	30	2.06	0.94	73.5	5.7	54.0	1820
S. F.	M	43	1.93	0.90	52.0	4.7	45.0	1820
T. B.	M	35	2.03	1.07	60.0	5.6	52.0	1830
F. P.*	M	36	1.87	0.80	62.5	5.6	40.0	1860
J. E.	M	49	1.84	0.66	58.5	4.0	44.0	1860
J. B.	M	33	1.69	0.90	49.5	5.1	39.5	1880
S. G.	M	29	1.93	1.20	34.5	5.0	36.0	1900
J. Ed.	M	47	1.81	0.68	43.0	3.2	43.0	1920
C. M.*	M	43	2.21	1.57	41.5	6.7	46.5	1930
C. N.	M	25	1.86	1.05	50.0	5.5	45.5	1940
J. C.	M	22	1.77	1.34	47.0	6.7	48.0	2030
V. C.	M	23	1.94	0.70	71.0	6.0	41.0	2050
J. L.	M	20	2.15	0.69	87.0	5.8	52.5	2060
J. B.	M	31	2.03	0.60	58.5	3.7	49.0	2060
B. B.	M	45	1.66	0.70	39.0	3.2	46.0	2080
J. B.	M	22	1.98	0.50	90.0	5.3	45.0	2110
D. O'B.	M	20	1.68	0.66	54.0	4.6	40.0	2150
F. D.	M	30	1.96	1.17	46.0	6.0	48.0	2160
O. G.	M	24	1.78	1.05	42.0	5.4	49.0	2370

All values were obtained at bromsulfalein plasma levels changing no more than 0.005 mg. per cent per minute, and were rounded off after calculation was completed.

P_{BSP} = plasma concentration of BSP

E_{BSP} = hepatic extraction of BSP

R_{BSP} = hepatic BSP removal rate

EHBF = estimated hepatic blood flow

* Subjects in whom uncomplicated hypertensive vascular disease was demonstrable.

TABLE 2.—*Estimated Hepatic Blood Flow in Hepatic Cirrhosis*

Subjects	Sex	Age	Surface area	P_{BSP}	ΔP	E_{BSP}	R_{BSP}	Hematocrit	EHBF
				Laennec's Cirrhosis—History of Chronic Alcoholism					
		yrs.	M^2	*mg.%*	*mg.%/min.*	%	*mg./min.*	%	*ml./min.*
W. P.	M	49	1.82	1.31	+0.005	24.0	1.3	44.0	750
G. G.	M	39	1.87	1.03	+0.002	39.5	2.0	37.0	790
I. C.	F	46	1.54	2.64	000	17.5	2.4	37.0	810
C. S.	F	48	1.54	2.43	+0.020	20.5	2.3	43.0	820
H. D.	M	51	1.79	3.18	−0.010	13.5	2.4	36.0	860
R. W.	M	54	1.84	2.53	−0.005	19.0	2.2	50.0	930
J. E.	M	39	1.94	2.88	+0.005	19.0	3.7	29.0	960
E. Mc.	F	67	1.80	2.15	+0.005	16.0	1.9	44.0	980
R. B.	M	40	1.66	1.32	+0.006	36.0	2.8	42.0	990
N. F.	M	31	1.91	0.54	−0.002	52.0	1.7	42.0	1050
E. G.	M	39	1.96	0.85	−0.006	33.0	2.0	44.0	1280
J. C.	M	61	1.93	1.48	+0.005	21.5	2.7	34.5	1320
H. D.	M	33	1.68	1.67	+0.005	25.5	3.5	49.0	1600
F. F.	M	43	1.59	0.50	−0.003	44.5	1.9	47.0	1600
E. K.	M	55	1.74	0.77	+0.030	25.0	1.8	47.0	1780
D. C.	F	38	1.82	1.55	+0.010	10.0	1.9	36.0	1910
O. H.	M	38	1.65	1.09	000	23.0	2.5	49.0	1990
				Laennec's Cirrhosis—Without History of Chronic Alcoholism					
I. N.	F	19	1.86	1.87	−0.005	24.0	2.3	30.0	730
N. W.	F	47	1.43	4.30	+0.010	12.0	2.4	41.0	780
S. G.	M	47	1.81	0.69	−0.003	20.0	0.7	36.0	780
A. R.	M	54	1.67	1.28	+0.005	26.0	2.0	36.0	940
P. P.	M	22	1.72	1.49	000	11.5	1.1	35.0	960
K. N.	F	38	1.52	1.85	+0.030	12.0	1.4	40.0	1030
P. Mc.	M	22	1.59	1.32	+0.002	32.0	2.5	42.0	1030
P. N.	M	20	1.78	1.50	+0.040	11.0	1.3	36.0	1220
N. D.	M	32	2.03	1.33	+0.005	34.0	3.4	44.0	1310
S. W.	M	28	1.57	0.83	+0.001	26.0	1.7	41.0	1330
H. C.	M	24	1.82	0.63	+0.001	45.0	2.3	39.0	1340
T. K.	M	24	1.90	0.83	+0.010	42.0	3.5	41.0	1720
				Biliary Cirrhosis					
F. G.	F	52	1.62	1.90	+0.010	12.0	1.5	37.0	1030
				Syphilitic Cirrhosis					
J. L.	M	49	1.64	3.00	000	18.5	1.7	37.0	490
				Schistosomiasis					
V. Q.	F	46	1.53	2.00	−0.005	36.5	2.4	33.0	480
M. D.	M	34	1.44	0.72	000	59.5	2.0	44.0	840
H. R.	M	23	1.65	1.03	000	65.5	4.5	44.0	1190
A. O.	M	32	1.60	1.08	+0.002	45.5	3.8	40.0	1280
				Banti's Syndrome					
L. H.	M	17	1.67	1.04	−0.005	72.0	2.7	36.0	560
P. J.	M	32	1.73	1.36	+0.010	56.5	2.9	42.0	640
M. H.	F	23	1.74	0.77	−0.001	67.5	3.8	35.0	1120
J. J.	M	34	1.78	0.70	000	47.0	2.9	37.0	1380

All values were taken at points where bromsulfalein (BSP) plasma concentrations were changing least. Change in BSP concentration is noted under ΔP as mg. % per minute, and direction of the change is shown by the signs. All other abbreviations are as in table 1. Data obtained when E_{BSP} was less than 10 per cent above BSP plasma concentrations of 1 per cent and less than 15 per cent below levels of 1 mg. per cent have been excluded.

TABLE 3.—*Splanchnic Oxygen Metabolism*

Subjects	Sex	Age	Arterial		Hepatic venous		Splanchnic oxygen A–V difference	Splanchnic oxygen uptake	Splanchnic oxygen uptake per M.² body surface
			Oxygen content	Oxygen capacity	Oxygen content	Oxygen saturation			
In Normal Men									
		yrs.	*ml.%*	*ml.%*	*ml.%*	*%*	*ml.%*	*ml./min.*	*ml./min./M.²*
M. G.	F	36	18.8	19.9	16.5	83.0	2.3	—	—
D. O'B.	M	20	15.4	16.1	12.8	79.5	2.6	46.6	27.8
M. G.	F	28	15.5	16.5	12.9	78.2	2.6	—	—
J. E.	M	49	17.4	18.1	14.7	81.4	2.7	51.6	28.0
H. N.	M	30	13.0	13.7	10.2	74.5	2.8	—	—
G. N.	M	26	16.7	21.0	13.7	65.2	3.0	—	—
K. Mc.	F	46	14.4	14.4	11.3	76.0	3.1	38.4	29.1
A. S.	M	24	18.2	19.1	15.1	79.0	3.1	53.6	28.8
J. P.	M	37	15.7	16.2	12.4	76.5	3.3	59.7	37.3
A. B.	M	41	17.7	18.7	14.4	77.0	3.3	49.5	28.4
A. W.	M	43	15.8	16.6	12.3	74.0	3.5	—	—
T. P.	M	29	19.4	20.0	15.7	78.5	3.7	—	—
J. D.	M	49	18.7	19.9	15.0	75.4	3.7	58.8	33.6
R. L.	M	26	15.1	15.8	11.4	72.2	3.7	—	—
M. G.	M	40	16.1	17.6	12.3	70.0	3.8	—	—
E. W.	F	33	12.7	13.7	8.9	65.0	3.8	68.0	41.2
L. C.	M	41	17.8	18.5	12.9	69.7	3.9	—	—
S. F.	M	43	18.1	19.0	14.0	73.6	4.1	74.5	38.6
T. D.	F	38	13.4	14.1	9.3	66.0	4.1	—	—
M. H.	M	24	17.9	18.6	13.8	74.3	4.1	62.7	30.4
S. D.	F	36	15.3	16.6	11.0	66.3	4.3	—	—
J. B.	M	31	19.0	19.7	14.7	74.6	4.3	88.6	41.2
D. P.	M	43	17.4	17.6	13.0	74.0	4.4	—	—
T. B.	M	35	18.5	19.9	14.0	70.5	4.5	82.4	40.6
J. W.	M	39	11.2	12.5	7.0	56.0	5.5	—	—
L. S.	M	50	18.2	19.1	12.5	65.5	5.7	98.5	58.0
I. T.	M	49	19.5	21.5	13.8	64.2	5.7	—	—
In Hepatic Cirrhosis									
Laennec's Cirrhosis—History of Chronic Alcoholism									
J. E.	M	39	10.8	11.2	17.7	68.7	3.1	29.8	15.3
L. R.	M	65	16.0	17.6	12.9	73.3	3.1	—	—
K. C.	F	50	15.4	17.2	11.9	69.7	3.5	—	—
N. F.	M	31	17.8	18.5	14.2	76.8	3.6	37.8	19.8
L. W.	F	33	16.3	17.7	12.6	71.3	3.7	—	—
H. D.	M	33	18.2	19.1	14.0	73.3	4.2	67.2	40.0
P. M.	M	63	15.8	16.6	11.2	68.8	4.6	—	—
E. K.	M	55	18.5	20.6	13.8	67.0	4.7	83.6	48.1
D. C.	F	38	14.6	15.3	9.5	62.0	5.1	97.4	53.5
F. F.	M	43	17.4	18.5	12.0	64.8	5.4	86.4	54.3
R. W.	M	54	19.4	20.7	13.9	67.1	5.5	51.2	27.8
S. G.	M	47	11.9	13.1	6.4	48.9	5.5	—	—
L. A.	M	60	13.9	15.8	8.3	52.5	5.6	—	—
E. G.	M	39	15.9	17.5	10.2	58.2	5.7	—	—
C. S.	F	48	16.0	17.5	9.3	53.3	6.7	55.0	35.7
G. G.	M	39	14.3	15.3	6.4	42.7	7.9	62.4	33.4

TABLE 3—*Continued*

Subjects	Sex	Age	Arterial		Hepatic venous		Splanchnic oxygen A–V difference	Splanchnic oxygen uptake	Splanchnic oxygen uptake per M.² body surface
			Oxygen content	Oxygen capacity	Oxygen content	Oxygen saturation			
Laennec's Cirrhosis—Without History of Chronic Alcoholism									
		yrs.	*ml.%*	*ml.%*	*ml.%*	*%*	*ml.%*	*ml./min.*	*ml./min./M²*
S. W.	M	28	17.9	19.6	15.0	77.0	2.9	38.6	24.6
H. C.	M	24	14.2	15.2	10.9	71.8	3.3	44.2	24.3
K. N.	F	38	15.9	17.2	12.5	72.6	3.4	35.0	23.0
C. M.	M	42	14.5	15.8	10.8	68.5	3.7	—	—
T. K.	M	24	14.7	15.2	11.0	72.5	3.7	63.7	33.5
I. N.	F	19	13.1	13.6	9.3	68.5	3.8	27.7	14.9
A. R.	M	54	15.2	15.9	11.0	69.2	4.2	39.5	23.6
P. N.	M	20	15.6	16.5	11.4	69.0	4.2	51.2	28.8
N. W.	F	47	16.4	17.3	12.1	70.0	4.3	33.6	23.4
N. D.	M	32	18.6	19.6	14.1	72.0	4.5	59.0	29.0
P. Mc.	M	22	15.5	16.3	10.9	67.0	4.6	47.4	29.8
P. P.	M	22	13.3	14.1	8.4	59.5	4.9	47.0	27.4
K. O'D.	F	20	16.5	17.6	11.4	64.8	5.1	—	—
R. Mc.	M	30	16.2	17.1	11.0	64.5	5.2	—	—
B. M.	M	46	11.8	12.0	6.6	55.0	5.2	—	—
Schistosomiasis									
H. R.	M	23	18.8	19.4	15.1	77.8	3.7	44.0	26.7
V. Q.	F	46	12.2	13.0	5.7	43.3	6.5	31.2	20.4
M. D.	M	34	14.8	15.6	7.8	50.0	7.0	58.8	40.8
Biliary Cirrhosis									
F. G.	F	52	15.6	16.4	10.8	65.9	4.8	49.5	30.5
Syphilitic Cirrhosis									
J. L.	M	50	14.3	15.1	8.6	56.9	5.7	27.9	17.0
Banti's Syndrome									
J. D.	M	33	6.6	7.7	2.7	33.8	3.9	—	—
M. H.	F	23	13.3	13.8	9.3	67.8	4.0	44.8	25.8
L. H.	M	17	13.9	14.8	9.0	60.7	4.9	27.4	16.4
P. J.	M	32	16.9	17.0	11.0	64.7	5.9	37.8	21.8
J. J.	M	34	14.7	15.6	8.6	55.0	6.1	84.2	47.3

Splanchnic oxygen consumption was calculated as the product of hepatic blood flow and splanchnic oxygen arteriovenous difference.

In normal persons removal of bromsulfalein in the splanchnic bed outside the liver is of no importance because the portal venous blood is returned to the heart almost entirely by way of the hepatic veins. This is no longer true in cirrhosis where an elaborate collateral venous system has been established. However, determination of the bromsulfalein content of portal and peripheral venous blood obtained simultaneously at operation in two patients with cirrhotic disease failed to disclose any significant difference. The possibility of enterohepatic circulation of bromsulfalein likewise has no practical importance in normal subjects because the hepatic venous bromsulfalein concentration in these and other studies has always been lower than the peripheral venous or arterial concentrations. In the presence of cirrhosis, this becomes a matter of great importance because direct return of dye from the

intestine to the systemic circuit by way of the portal venous collaterals would be equivalent to administration of a second bromsulfalein infusion of unaccountable size. As a result, estimations of bromsulfalein removal would be erroneously low. However, oral administration of large doses of bromsulfalein (500 mg.) to four patients with large functioning portocaval anastomoses failed to produce detectable concentrations of bromsulfalein in the peripheral blood within 45 minutes. Lorber and Shay[11] have reported observations of low concentrations of dye in the blood of normal individuals 30 minutes after introducing doses of from 2 to 5 mg. per Kg. of body weight into the duodenum, but they state that amounts equivalent to an intravenous dose of 2 mg. bromsulfalein per Kg. of body weight does not result in significant enterohepatic circulation. Since subjects with cirrhosis excrete the dye slowly and in small amounts it is probable that little of it is available for enterohepatic circulation during the measurement of hepatic blood flow. The priming dose is usually no more than 2 mg. per Kg. of body weight and the plasma concentration is maintained at a relatively low level. Finally, as noted above, the portal venous bromsulfalein concentration does not appear to differ from peripheral venous concentration. Hence, it seems most unlikely that enterohepatic circulation introduces a significant error into the calculation of hepatic blood flow in cirrhotic patients.

The problem of extrahepatic removal of bromsulfalein becomes a matter of major concern in evaluating the measurement of hepatic blood flow in cirrhosis because the hepatic removal is greatly reduced, whereas extrahepatic extraction probably remains unchanged, thus contributing more importantly to the total removal of dye than in the normal. It has been recognized from the outset[7] that extrahepatic removal of bromsulfalein from the blood must occur, but it has been considered insignificant because most of the injected dye is excreted in the bile. Cohn and his co-workers[12, 13] have shown that the extrahepatic bromsulfalein removal may be quite large in absolute terms

TABLE 4.—*Statistical Analysis of Data in Tables 1 to 3*

	Normal			Cirrhosis		
	Male	Female	Total	Male	Female	Total
Estimated Hepatic Blood Flow						
No. of observations	73	18	91	29	10	39
Mean (ml./min.)	1580	1340	1530	1140	970	1090
Range (ml./min.)	970–2370	1000–1790	970–2370	490–1990	480–1910	480–1990
σ	±280	±200	±300	±350	±360	±380
σ_m	±325	± 46.6	± 31.5	± 65	±114	± 60.8
Hepatic Bromsulfalein Extraction						
No. of observations	73	18	91	29	10	39
Mean (%)	61	55	60	34	23	31
Range (%)	27–91	37–91.5	27–91.5	11–72	10–67.5	10–72
σ	±15.3	±15.3	±15.6	±16.2	±16.7	±17.3
σ_m	±1.8	±3.6	±1.6	±3.0	±5.3	±2.8
Hepatic Oxygen Arteriovenous Difference						
No. of observations	21	6	27	30	11	41
Mean (ml.%)	3.87	3.36	3.76	4.75	4.63	4.71
Range (ml.%)	2.8–5.8	2.3–4.3	2.3–5.8	2.9–7.9	3.4–6.7	2.9–7.9
σ	±0.76	±0.78	±0.71	±1.15	±1.08	±1.17
σ_m	±0.16	±0.34	±0.15	±0.21	±0.33	±0.18

but they have worked with high plasma concentrations of bromsulfalein. When the plasma bromsulfalein level was maintained between 1 and 2 mg. per 100 ml. in dogs before and after evisceration, extrahepatic removal (determined after evisceration) was found to be less than 5 per cent of the total preoperative removal rate at the same blood level.[10] It is evident, therefore, that the error introduced by extrahepatic removal is less than that introduced by other factors such as failure to sample mixed hepatic venous blood. It has seemed reasonable to accept the hepatic removal rate determined on the basis of the infusion rate at a more or less constant plasma bromsulfalein concentration of less than 3 mg. per 100 ml. as sufficiently accurate for the purposes of this study.

Results

An evaluation of the hepatic circulation can only be made against the background provided by an analysis of values obtained in a similar but "normal" population, that is, "normal" with respect to hepatic function and circulation. Table 1 contains values for hepatic blood flow measured in 91 individuals free of hepatic and cardiovascular disorders with the exception of 11 who had uncomplicated hypertensive vascular disease. Since the group with hypertensive disease did not differ in any statistically significant manner from the remainder, the figures are considered as a whole. Estimated hepatic blood flow averaged 1530 ml. per minute with a standard deviation of ±300 ml. per minute, ranging from 970 to 2370 ml. per minute (table 4). Analysis of variance failed to reveal any consistent or statistically significant difference between groups studied in sequence that could be attributed to change in technic, the hospital population, method of selection, or to other causes. Hence the figures are arranged in all the tables in ascending order with respect to hepatic blood flow or arteriovenous oxygen difference. It may be seen that they are rather symmetrically distributed about the mean of 1530 in table 1. The tendency for the figures in females to fall below the total mean is evidence of a significant sex difference. The mean figures for hepatic blood flow in 18 females was 1340 ml. per minute and in 73 males 1580 per minute (table 4). The difference between these two groups was highly significant, amounting to more than four times the standard error of the difference (relative deviate, $dev/\sigma = 4.0$). The figures for hepatic blood flow were not significantly correlated with body surface (S.A.) and consequently have not been adjusted for variation in body surface.

Inspection of the figures for plasma concentration of bromsulfalein (P_{BSP}) at the time of hepatic blood flow (EHBF) measurement suggests that higher values of hepatic blood flow are frequently associated with low plasma levels of bromsulfalein. Sherlock[14] has found a good negative correlation between plasma concentration of bromsulfalein and hepatic blood flow in her studies of normal subjects, and she suggests that the higher values obtained for hepatic blood flow when the plasma concentration of bromsulfalein is less than 1 mg. per 100 ml. may be erroneous because of augmented extrahepatic bromsulfalein uptake at low plasma concentrations. There is no direct evidence in favor of this contention and statistical analysis of the values in table 1 fails to lend it support. A slight but statistically significant negative correlation obtains between all figures for plasma concentration of bromsulfalein and hepatic blood flow ($r = .49$) but no correlation ($r = -.03$) was demonstrable between these values at bromsulfalein concentrations equal to or less than 1 mg. per 100 ml. The negative correlation for the group as a whole is best explained on technical grounds. The rate of bromsulfalein infusion does not vary greatly from subject to subject and in consequence higher bromsulfalein concentrations tend to occur in individuals with low hepatic blood flow than in those with high flow at equilibrium. Although bromsulfalein extraction is to some extent a function of the concentration in the plasma, it ranged much more widely than the concentration. Bromsulfalein extraction was less on the average in females (55 per cent) than in males (61 per cent) but the difference was not significant ($dev/\sigma = 1.4$). Mean bromsulfalein extraction for the total group was 60.0 ± 15.6 per 100 ml. (table 4).

The data obtained in studies of patients with

cirrhotic disease are set forth in table 2 according to cause. Since the values for mean hepatic blood flow in the different groups do not differ significantly and since all these disorders have in common a reduction of portal venous inflow and real or potential cirrhosis all figures have been treated en masse as representative of a population ("cirrhotics") sufficiently homogeneous and distinctive for the purposes of this investigation. Indeed, cirrhotic disease was demonstrable by biopsy or necropsy in nearly all these individuals except in those with Banti's syndrome due to extrahepatic portal venous obstruction. The latter have been included in the group as a whole because the circulatory disturbance resembles that of the others and because cirrhosis ultimately develops in many patients and may have been present in early form undetectable by biopsy or gross appearance. The similarities between the groupings in table 2 indicate that, regardless of cause, cirrhotic disease produces similar hepatic circulatory effects. With expansion of these groups, it is possible, of course, that a more subtle diversification not at present apparent may be demonstrable, but these theoretic dissimilarities are not germane to the broader issues with which this analysis is concerned.

Estimated hepatic blood flow ranged from 480 to 1990 ml. per minute among the "cirrhotics" and averaged 1090 ± 380 ml. per minute (table 4). The difference between the "cirrhotic" and "normal" mean values for hepatic blood flow was highly significant, amounting to 6.4 times the standard error of the difference. As among the normal subjects, a sex difference was apparent, mean hepatic blood flow in women averaging 970 ml. per minute as against 1140 ml. per minute for males, but it was not statistically significant. Mean hepatic bromsulfalein extraction among "cirrhotics" (31.4 ± 17.3 per cent) differed significantly from the normal (dev/σ = 9.0). Since the plasma concentration of bromsulfalein varied through the same range among these individuals as in the normals, this deviation could not be attributed to a higher bromsulfalein blood level. Women again were found to have lower, but not significantly lower, values for bromsulfalein extraction than men (mean equal to 23.0 per cent in contrast to 34.0 per cent). In summary, then, it may be concluded that hepatic blood flow is significantly reduced in cirrhotic disease in association with diminished hepatocellular ability to remove bromsulfalein from the blood.

The difference in oxygen content between arterial and hepatic venous blood is equal to the amount of oxygen taken up by all the tissues supplied by the arteries feeding the portal venous system. This value is therefore a function of the total splanchnic oxygen consumption which may be estimated by multiplying hepatic blood flow and the hepatic arteriovenous oxygen difference in the normal person. But in the "cirrhotic" an appreciable volume of blood escapes from the portal vein through anastomotic channels and cannot contribute either to calculated hepatic blood flow or to hepatic arteriovenous oxygen difference. Recent studies[15, 16] have revealed that the oxygen content of portal venous blood is high and that the oxygen uptake of splenic and gastrointestinal tissues is slight in resting, fasting individuals. It could be argued, therefore, that the values obtained under the conditions of this study reflect predominantly hepatic oxygen uptake in normals as well as "cirrhotics" and that loss of portal blood through anastomotic channels does not significantly affect the final figure.

Hepatic arteriovenous oxygen differences in normal subjects (table 3) ranged from 2.3 to 5.8 ml. per 100 ml. and averaged 3.76 ± 0.71 ml. per 100 ml. (table 4). Again the figures for women were less but not significantly less than those for men (mean for women equal to 3.36 ml. per 100 ml., and for men 3.87 ml. per 100 ml.). Among "cirrhotics" the hepatic arteriovenous oxygen difference was 4.71 ± 1.17 ml. per 100 ml. on the average, significantly higher than the normal mean (dev/σ = 3.8). An insignificant sex difference again favoring the males was demonstrable (table 4). In contrast, calculation of "splanchnic oxygen consumption" in 13 normal subjects and 30 cirrhotic patients in whom hepatic blood flow and hepatic oxygen arteriovenous difference were determined simultaneously, revealed dissimilarity between the two groups of borderline significance. These values averaged 64.1 ± 16.8

ml. per minute in the normal subjects and 51.2 ± 19.1 ml. per minute in the cirrhotic patients ($dev/\sigma = 2.2$). When calculated on the basis of body surface area, the deviation was even less marked, 35.6 ± 8.3 ml. oxygen per minute per square meter of body surface in normals and 29.8 ± 10.6 ml. per minute per square meter in "cirrhotics" ($dev/\sigma = 1.9$). The slightly lower value for oxygen consumption observed in "cirrhotics" might be attributable to loss of portal blood through collateral channels.

Comment

The findings of this study indicate that hepatic blood flow is reduced in the presence of any cirrhotic process. The elevation in hepatic arteriovenous oxygen difference in the absence of increased total oxygen consumption suggests that slower perfusion of the liver with prolonged contact between cells and blood may permit more efficient extraction of oxygen. In consequence hepatic venous oxygen content would fall as observed, and the oxygen tension in fluids bathing the cells would be reduced. The fact that bromsulfalein extraction and removal rate were uniformly diminished may be explained by the destruction of extracting cells or by a selective disturbance in the mechanisms of bromsulfalein transfer. Both factors were probably involved. Ample evidence of liver damage was available in nearly every instance. Brauer and his associates[17] has shown that bromsulfalein uptake by liver cells proceeds independently of oxidative activity and since the hemodynamic changes that favored relative enhancement of oxygen extraction should also have improved bromsulfalein uptake it may be inferred that bromsulfalein transport into the bile was selectively depressed. On the other hand oxygen uptake per unit of functioning cell mass must have actually increased since calculated oxygen consumption remained within normal limits despite extensive parenchymal damage.

The relative contributions of the portal venous and hepatic arterial circulations cannot be accurately assessed. It seems unlikely, however, that diminished hepatic arteriolar resistance leads to an absolute increase in arterial inflow at the expense of the portal venous input, since one would expect under these circumstances an elevation, not a reduction, in estimated hepatic blood flow and a fall, not an increase, in hepatic arteriovenous oxygen difference. Though the fraction of arterial blood contributing to hepatic venous outflow probably rose, there is no evidence that it exceeded, or even kept pace with, the tissue demand for oxygen and, presumably, other materials.

Hepatic ischemia and relative tissue hypoxia appear to be characteristic stigmas of cirrhotic disease. Whether these precede or follow the destruction of hepatic cells and the proliferation of connective tissue must remain unsettled. It is tempting to speculate on the possibility that the changes in hepatocellular oxygen metabolism and bromsulfalein transport may reflect some serious derangement of cellular physiology that is ultimately followed by necrobiosis and changes in the tissue structure and vascular architecture of the liver.

The data presented here have been derived from a heterogeneous group of patients with different diseases and in different phases of the same disease. Furthermore, the criteria for selection eliminated from consideration those patients with jaundice or excessive disturbance of bromsulfalein removal. It should be emphasized therefore that the preceding discussion applies to cirrhosis in general. It should not be interpreted as precluding the possibility that hyperemia and diverse changes in oxygen and bromsulfalein extraction might occur in certain types or at certain stages. Additional data are required to permit more particularizing statements regarding the discrete effects of such factors as ascites, recent hemorrhage, biliary obstruction and specific etiologies.

Summary

The hepatic blood flow (EHBF) has been estimated by the bromsulfalein (BSP) clearance method in 91 normal human subjects and in 39 patients with various kinds of cirrhotic disease, including four with Banti's syndrome due to extrahepatic portal venous obstruction. The hepatic arteriovenous oxygen difference was also determined in 27 normal and 41 cirrhotic sub-

jects, in 13 and 30, respectively, of whom hepatic blood flow was measured simultaneously.

Mean hepatic blood flow was 1530 ± 300 ml. per minute in the normal and 1090 ± 380 ml. per minute in the cirrhotic. This reduction in hepatic blood flow was highly significant and it was associated with a marked fall in hepatic bromsulfalein extraction, 60 ± 15.6 per cent, normal, and 31 ± 17.3 per cent, cirrhotic.

The hepatic arteriovenous oxygen difference, on the other hand, rose significantly among the cirrhotics (41 patients) from a normal (27 individuals) mean of 3.76 ± 0.71 ml. per 100 ml. to 4.71 ± 1.17 ml. per 100 ml. as a result of a decrement in hepatic venous oxygen concentration. Calculated hepatic oxygen consumption, however, did not differ much from the normal.

Acknowledgment

The authors wish to acknowledge their debt to Misses Lottie Fogel, Joan Hunt, and Mrs. Edgar Baker for technical assistance, to Drs. R. W. Williams, A. E. Groff, and many others for professional help and to Dr. John Fertig for advice in the statistical analysis.

REFERENCES

[1] McIndoe, A. H.: Vascular lesions of portal cirrhosis. Arch. Path. **5:** 23, 1928.

[2] Lichtman, S. S.: Diseases of the Liver, Gall-Bladder and Bile Ducts. Philadelphia, Lea and Febiger, 1949.

[3] Kelty, R. H., Baggenstoss, A. H., and Butt, H. R.: The relation of the regenerated hepatic nodule to the vascular bed in cirrhosis. Proc. Staff Meet. Mayo Clinic **25:** 17, 1950.

[4] Herrick, F. C.: An experimental study into the cause of the increased portal pressure in portal cirrhosis. J. Exper. Med. **9:** 93, 1907.

[5] Dock, W.: Role of increased hepatic arterial flow in the portal hypertension of cirrhosis. Tr. A. Am. Physicians **57:** 302, 1942.

[6] Cournand, A., and Ranges, H. A.: Catheterization of right auricle in man. Proc. Soc. Exper. Biol. & Med. **46:** 462, 1941.

[7] Bradley, S. E., Ingelfinger, F. J., Bradley G. P., and Curry, J. J.: Estimation of the hepatic blood flow in man. J. Clin. Investigation **24:** 890, 1945.

[8] Bradley, S. E., Ingelfinger, F. J., Groff, A. E., and Bradley, G. P.: Estimated hepatic blood flow and hepatic venous oxygen content in cirrhosis of the liver. Proc. Soc. Exper. Biol. & Med. **67:** 206, 1948.

[9] Van Slyke, D. D., and Neill, J. M.: The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. I. J. Biol. Chem. **61:** 523, 1924.

[10] Bradley, S. E.: Clinical aspects of hepatic vascular physiology. Tr. Josiah Macy Jr. Foundation Conference on Liver Injury **9:** 71, 1950.

[11] Lorber, S. H., and Shay, H.: Entero-hepatic circulation of bromsulfalein. J. Clin. Investigation **29:** 831, 1950.

[12] Cohn, C., Levine, R., and Streicher, D.: The rate of removal of intravenously injected bromsulphalein by the liver and extra-hepatic tissues of the dog. Am. J. Physiol. **150:** 299, 1947.

[13] Cohn, C., Levine, R., and Kolinsky, M.: Hepatic and peripheral removal rates in the dog, for intravenously injected bromsulphalein. Am. J. Physiol. **155:** 286, 1948.

[14] Sherlock, S., Bearn, A. G., Billing, B. H., and Paterson, J. C. S.: Splanchnic blood flow in man by the bromsulfalein method, the relation of peripheral plasma bromsulfalein level to the calculated flow. J. Lab. & Clin. Med. **35:** 923, 1950.

[15] Myers, J. D.: The hepatic blood flow in Laennec's cirrhosis, with an estimate of the relative contributions from portal vein and hepatic artery. J. Clin. Investigation **29:** 836, 1950.

[16] Smythe, C. McC., Fitzpatrick, H. F., and Blakemore, A. H.: Studies of portal venous oxygen content in unanesthetized man. J. Clin. Investigation **30:** 674, 1951.

[17] Brauer, R. W., and Pessotti, R. L.: The removal of bromsulphthalein from blood plasma by the liver of the rat. J. Pharmacol. & Exper. Therap. **97:** 358, 1949.

A Newly Modified Electromagnetic Blood Flowmeter Capable of High Fidelity Flow Registration

By ALFRED W. RICHARDSON, PH.D., ADAM B. DENISON, JR., M.D., AND HAROLD D. GREEN, M.D.

This paper describes a meter which, when inserted into an artery or vein, is capable of measuring the average flow, or the "instantaneous" flow throughout the heart cycle. Flow is recorded with a direct-writing instrument.

THE GENERAL principle of the electromagnetic flowmeter was developed independently by Kolin[1] in this country and by Wetterer[2] in Germany. The system described by Kolin utilized a direct current electromagnet and a direct current system of recording using either a D'Arsonval or an Einthoven string galvanometer without amplification. In 1937 Kolin and Katz[3, 4] modified the flowmeter by interrupting the pickup potential with a tuning fork, and feeding the alternating potentials into an A.C. amplifying system to be observed on an oscillograph. Jochim[5-7] modified Kolin's system by the use of a permanent magnet, closely fitting nonpolarizing electrodes, and a direct current type direct-coupled amplifier. In 1941[8] and again in 1945, Kolin[9] modified his instrument by substituting a 60 cycle alternating current magnet. This arrangement furnished a sinusoidal voltage in the input of the amplifier, which was modulated by the blood flow. A coil of wire around an arm of the magnet was used to buck out the voltage generated in the pickup at zero flow. To compensate for harmonics and phase shift, a filter was placed between the second and third stages of the amplifier. This meter, as previous ones, was designed to measure flow on the unopened blood vessel, and recording was accomplished by photographing a segment of the wave peak on an oscillograph.

In 1949, in an attempt to adapt a reproduction of the Kolin flowmeter to physiologic measurement, Richardson, Randall and Hines[10] found it insufficiently stable and practical. This group developed a method of potential pickup that employed a cannula with imbedded electrodes which they used with the more adaptable alternating current system. The system featured an amplifier with sufficient gain to use a 5 milliampere ink-writing recorder. This flowmeter was found to have negligible drift and to be accurate to less than 5 per cent error with forward flow, but was not capable of a linear reproduction of backflow and was not adaptable to be used with high-speed pen recorders of greater internal resistance.

In view of the new potentialities of this method of blood flow measurement, it was thought to be of value to modify further the system of Richardson, Randall and Hines,[10] attempting to preserve its desirable features while altering the less desirable characteristics. This newly modified instrument has been found extremely practical in use. It possesses negligible instability, records flow linearly both forward and backward with an error of less than ±5 per cent and can be adapted to a wide range of pen recorders of various speeds and internal resistances.

PRINCIPLE

When an electric conductor such as blood moves across the lines of force of a magnetic field, a potential difference is created in the conductor. If the field is uniform, and the conductor moves in an axis at right angles to the axis of the magnetic field, the electromotive force generated will be directly proportional to field strength, the speed of the conductor,

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and the length of the conductor across the field and will be directed at right angles to the direction of movement and to the axis of the magnetic lines of force.

The potential (E) generated in the conductor will then be:

$$E = B \cdot l \cdot \bar{v} \cdot 10^{-8}$$

Where E is the potential difference in volts; B, field strength in gauss, l, length of the conductor across the field in centimeters (between the electrodes); and $\bar{v}$, speed of the conductor in centimeters per second. In a blood flow system, $\bar{v}$ is approximately the average velocity of flow across l in the cannula, and l is approximately the internal diameter of the cannula.

Therefore,

$$E = \bar{v} \cdot K$$

where $K = B \cdot l \cdot 10^{-8}$, and $\bar{v}$ = the average velocity of flow across l. By use of a 60 cycle A. C. system, including a 60 cycle A. C. magnet, an additional constant is to be taken into account because the electrodes and their leads act as a one-turn transformer in which an additional (A) voltage is generated. Therefore, the total potential (E') in the amplifier input leads is

$$E' = E + A$$

The A voltage is proportional to B, the field strength, and is about 90 degrees out of phase with the E voltage generated by the flow. In order to cancel out the A voltage, a single turn of wire is wound about one arm of the magnet and led into the instrument to supply a bucking voltage. This bucking voltage, which is about 180 degrees out of phase with the A voltage, is passed through a variable resistance to control its magnitude and is balanced at the input of the second stage of the amplifier against the A voltage from the leads. Under this condition, with the exception of possible harmonics in the system, the output will read zero when flow is zero. However, if the phase of the bucking voltage is adjusted by additional capacitance, a controlled forcing potential which is in phase with the flow (90 degrees from A voltage), may be applied to the second stage of the amplifier. Back flow then may be measured in this system up to a value not to exceed this controlled forcing potential. If backflow should exceed this value it will be distorted, but since this controlled forcing potential may be increased to the full scale of the system, backflow equal to the full value of forward flow can be recorded as a linear function of flow.

Materials and Methods

Description of Apparatus. The complete flowmeter consists of a specially constructed plastic cannula which possesses relatively nonwettable properties, an A. C. magnet, a newly designed A. C. amplifier, and an Esterline-Angus 5 milliampere recorder or a Brush magnetic recorder.

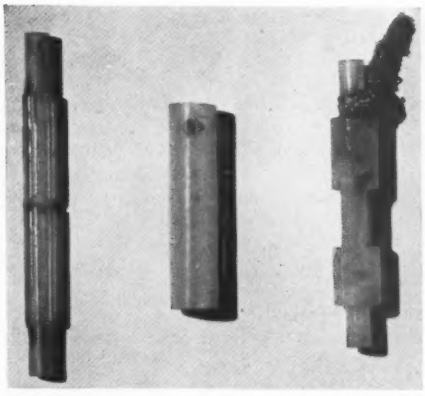

Fig. 1. Photograph of plastic cannula used with electromagnetic flowmeter, showing the elements of construction.

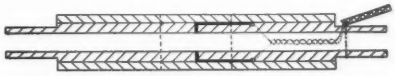

Fig. 2. Schematic diagram of plastic cannula showing the positioning of the gold electrodes.

The Cannula. The cannula structure consists of a Polystyrene or Plexiglas tube with an internal diameter equal to or slightly greater than the lumen of the blood vessel to be cannulated. While smaller sizes are adaptable to the instrument, they would increase unduly the frictional resistance to flow in the fluid system, thereby introducing an undesired error.[11] A cannula such as found in figure 1, which has a lumen 3 mm. in diameter, is quite satisfactory for use in the femoral artery of a dog. This particular model is 5 cm. long with a 3 cm. plastic sleeve fitted over the middle section in such a manner that the leads from both the pickup electrodes and the ground traverse between the two pieces of tubing. The detailed construction is revealed better in figure 2. In the middle of the cannula are two gold

wire tips, shown at the top and the bottom diametrically opposed to each other, which serve to pick up the *E* potential generated in the magnetic field by the blood flow. These tips of noncorrosive and highly conductive metal just touch the periphery of the lumen. Onto these tips just outside the inner tubing are soldered the two pickup leads which are then tightly twisted and passed down the cannula in a precut groove, into a shielded cable which runs to the amplifier input connection. In addition to these leads, two gold tips are imbedded in the inner cannula tubing, bilaterally and equidistant from the magnet, and these are soldered to a single fine silver or tinned copper wire which in turn is brought down a groove to the end of the cannula where it is joined to the shielding.

When the above connections are complete, the outer and inner surfaces of the inner and outer respective plastic tubes are coated with solvent, and the outer sleeve is slipped over the smaller inner one so that the two encompass the connections and hold them rigidly and permanently in position. When dried, a flat groove may be filed on each side of the outer tube to fit the jaws of the magnet, and the cannula is ready to use. In cannulating a vessel, a 3 mm. nonwettable flexible plastic tube may be stretched to fit over each end of the cannula and bent to go into the appropriate vessel. Operationally, this is more adequate than a rigid system of cannulation, because movements of the part do not affect the potential pickup.

The cannula and pickup incorporate the following desirable features: (a) an electrical pickup system well isolated electrically from the inconstant surrounding tissue conditions; (b) a lumen of uniform size to match the vessel size with negligible loss due to frictional resistance to flow; (c) a minimum of nonwettable surface with which the blood is in contact; (d) a rigid, nonvarying position of the pickup leads which prevents extraneous voltage variation from appearing on the recorder; (e) flexible cannula tips to allow work with moving tissues such as are encountered in recording coronary artery blood flow; and (f) a newly designed grounding system which further aids in eliminating extraneous potentials from the immediate vicinity of the cannula during measurement.

The Magnet. The A. C. magnet used with this meter is made by recutting the stacked laminations from a 4 by 3 inch transformer, the laminations being $\frac{3}{4}$ inch wide and $\frac{1}{16}$ inch thick. Eighteen laminations make the total magnet $\frac{1}{4}$ inch thick. The jaws of the magnet are tapered to $\frac{1}{2}$ inch width making the magnet tips $\frac{1}{2}$ by $\frac{1}{4}$ inch with an air space $\frac{1}{4}$ inch wide. The coil is constructed of 1400 turns of No. 22 wire excited with a 110 volt A. C. 60 cycles per second source. This gives a field of better than 1000 gauss across the poles. This magnet has been used with the meter successfully with or without a constant voltage regulator, although a regulator has obvious theoretic advantages, if its voltage wave form has a minimum of harmonics. However, the regulating transformer may produce enough second harmonic distortion to nullify the benefit obtained from its voltage stabilization.

The Amplifier. A diagram of the amplifier is shown in figure 3. It features a balanced push-pull circuit with the plate supply circuit +150 volts and the cathode supply −150 volts to achieve maximum stability. In the present form it is adaptable for 200 cycles per second or 60 cycles per second carrier frequency but the availability of a 60 cycles per second voltage source makes it more practical. On the other hand, the use of 200 cycles carrier frequency allows optimal gain with minimum recording of hum and allows recording of higher speed transients.

The amplifier consists of a series of A. C. stages followed by a tuned circuit resonant at the carrier frequency, a rectifier, and a D. C. current amplifier. The major modification of the basic circuit is the control of phase in the initial bucking potential stage. Here, a critical R-C circuit adjusts the bucking voltage phase to interact at the input to the second stage with the potentials originating in the cannula pickup so that backflow may be accurately reproduced as described. Another useful modification in this circuit is the balancing circuit in the rectifier stage which serves to cancel the zero flow forcing voltage, thereby allowing one to adjust the recording pen to a desired zero point when no flow is present, and to change the "D. C. gain" sensitivity without altering this zero. The bank of capacitance shunts just preceding the first D. C. stage aids in damping out pulsatile transients, making possible mean flow recording or critical damping when different recorders are employed. The series resistors at the output allow recorders of different internal resistance and different current or voltage sensitivity to be used.

It has been a practice to use this amplifier with a standard power supply using gaseous voltage regulating tubes, and to supply the filaments of the first three stages with 6 volt D. C. voltage to avoid 60 cycle A. C. voltages in these stages. This latter precaution is not necessary except at very high gain settings.

Adjustment of the instrument is accomplished most conveniently by use of an oscilloscope attached between a plate of the 6SN7 and ground, with the sweep synchronized with the supply frequency. A voltage is applied in phase with the flow-induced voltage until the pen is moved up to about one-half scale on the recorder. This will permit recording an equal amount of backflow if desired. The proper output resistance is selected, the zero line adjusted, the blood flow released, and the meter is in operation.

Calibration of the Instrument. The instrument may be calibrated by measuring the flow of blood out of the distal end of the cannula to which plastic

tubing is attached and run into a graduate; a clamp varies the diameter to achieve the desired range of flow rates. Since a point on the record will correspond to each flow rate, a curve of best fit may be drawn transecting these points and extrapolated to zero when plotted on graph paper.

Linearity. Figures 4 and 5 reveal the linear calibration curves as measured on the two recorders previously mentioned. It may be observed that backflow on these curves is in a linear relationship with forward flow. Measurement error, including observers' reading error, has been found to be less than ±5 per cent up to full scale deflection of the instrument.

Sensitivity. The maximum sensitivity which has been attained with this system, while at the same time maintaining the stability indicated below, is 3 milliamperes deflection from zero on a 5 milliampere Esterline-Angus recorder and 12 mm. on a Brush pen motor for a flow of 30 ml. per minute.

Constancy of Calibration. Base line deviation over a four hour period under constant test conditions is less than ±2 per cent as determined on the 5 milliampere recorder; and the deflection for a 60 ml. per minute flow remained within ±5 per cent for the same period. The flowmeter has been tested over the past 12 months on 95 experimental animals, using the same cannula for potential pickup. The system has maintained its sensitivity and base line

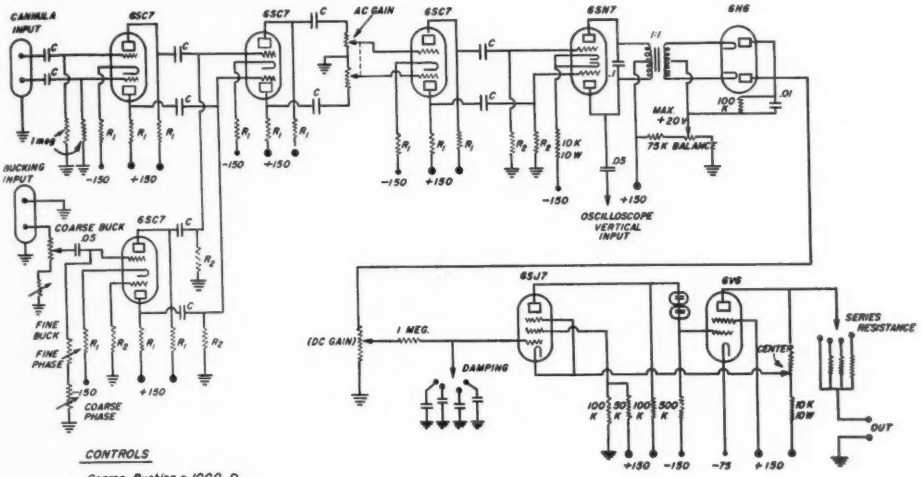

FIG. 3. Diagram of amplifier, complete, with the exception of the power supply.

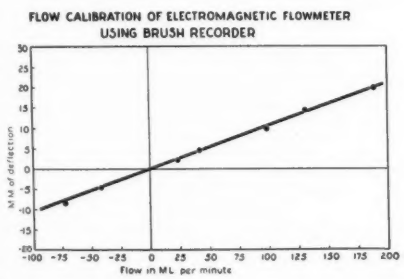

FIG. 4. Flow calibration of the flowmeter with the use of a Brush magnetic high speed recorder.

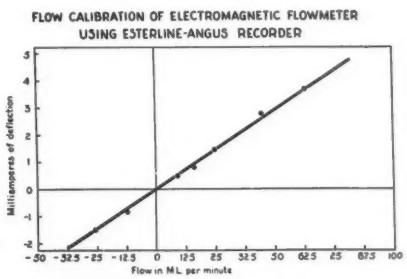

FIG. 5. Flow calibration of the flowmeter with the use of an Esterline-Angus 70 ohm, 5 milliampere, slow speed recorder.

stability within ±2 per cent during this period of time.

Flow Records

Mean Flow Records. This flowmeter as described is adaptable to be used with a 5 milliampere Esterline-Angus recorder, a Brush magnetic recorder, or others with similar characteristics. We have found the Esterline-Angus more practical for mean blood flow measurements where both the cardiac rate and true mean flow measurement are desired. A typical record showing a flow of 72 ml. per minute in the femoral artery of a dog and obtained by use of

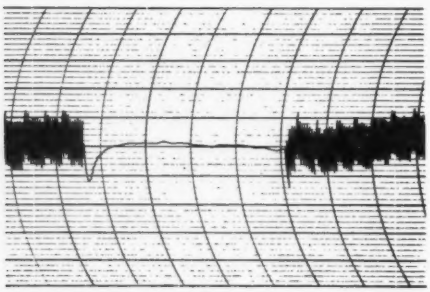

Fig. 6. Sample record showing pulse contour and electronically integrated mean flow as recorded on the 5 milliampere recorder.

the Esterline-Angus recorder is found in figure 6; this record demonstrates typical contours due to cardiac pulse and respirations as reflected in arterial flow, and then the altered contour when the rapid changes are integrated by damping electronically for mean flow measurement.

Instantaneous Flow Records. Fast recorders such as the Brush pen motor and the Sanborn direct writer may be used where it is desired to record high speed transients. Figure 7 shows a femoral artery flow of 62 ml. per minute as recorded or the Brush instrument revealing the detailed flow pattern with time. Fine lines on the abscissa equal one second. Figure 8 is a sample record of the output of a hydraulic square wave generator. The sharpness of the deflections, and the absence of lag and overshoot demonstrate the fidelity of reproduction of rapidly fluctuating forward and backward flow.

Pressure Loss. The loss in lateral pressure due to resistance to flow in this instrument amounts to less than 1 mm. Hg for a blood flow of 30 ml. per minute through the cannula alone. The pressure drop for the cannula plus connecting tubes, etc., is less than 3 mm. Hg for a flow of 30 ml. per minute.

Physiologic Flow Measurement. Since this system accurately measures high speed transients with critical damping, studies have been carried out in the femoral artery of the dog to

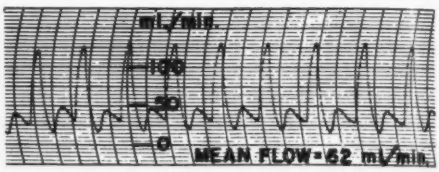

Fig. 7. Reproduced contours of typical control flow in the femoral artery as recorded on a Brush magnetic recorder. Five lines on the abscissa equal one second.

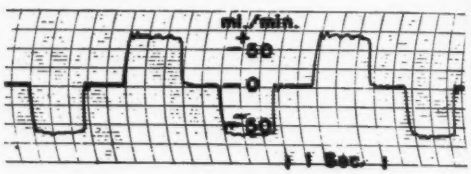

Fig. 8. Reproductions of the flow pattern created by a hydraulic square-wave generator with near-critical underdamping identical with the damping used in figure 7.

determine the flow pulse contour and to evaluate the possibilities of backflow in this vessel as reported by Shipley, Gregg, and Schroeder.[12] Figure 7 is a sample of femoral artery flow of 62 ml. per minute as recorded on a high speed Brush magnetic recorder. It may be observed in this record that backflow typically was not present in the femoral artery, although the flow rate approached zero at two points during the cardiac cycle. However, when 1.0 μg. of epinephrine was injected intra-arterially, with consequent increase in peripheral resistance and diminution in femoral arterial flow, backflow was observed to occur for a short time during each cardiac cycle (fig. 9). Such backflow-containing contours have been

observed for over five minutes following a single injection of 1.0 μg. of epinephrine.

Studies with other flowmeters in this laboratory which have been undamped or subdamped with a resultant characteristic of overshoot have shown that typical control blood flow in the femoral artery may be recorded so that there appear to be backflow when the flow rate approaches zero, due to distortion in the reproduced record. Critical damping, or even underdamping close to the critical point, of one of these systems (differential pressure flowmeter) eliminated this phenomenon of "backflow" and the contours closely resembled that shown in figure 7, recorded by the use of the

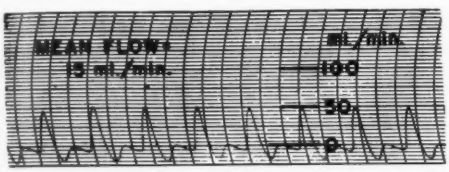

FIG. 9. Reproduced contours of flow in the femoral artery similar to figure 7 but preceded by the injection of 1 μg. of epinephrine intraarterially.

electromagnetic flowmeter. In keeping with a conservative analysis, the system was slightly undamped at a near-critical level for this recording.

In order to demonstrate the fidelity of this system under these circumstances, a hydraulic square-wave generator was attached to the cannula. The reproduced contours are presented in figure 8, where five lines on the abscissa represent one second. It may be seen that the system adequately reproduces the flow both forward and backwards with fidelity including the gross and minute transients in the hydraulic movement. The near-critical damping used here was identical with that used in the femoral flow contours shown in figure 7.

The hydraulic square-wave generator consisted of a 10 cc. syringe with the plunger attached to a dual set of metal racks in such a manner that a cog engaged each of the racks during 90 degrees of rotation alternately and was free before each alternate gear engagement. To facilitate this, the teeth were filed off three-fourths of the gear allowing it to engage during one-fourth of its rotation. Since one rack was situated above the gear and one rack was situated below, alternate engagements forced the syringe in opposite directions. With the syringe securely stabilized, this resulted in an abruptly generated forward and backward flow of fluid.

DISCUSSION

While this instrument was built to be a pulsatile flowmeter, the electronic damping selector built into the device makes it adaptable to mean flow measurement as well. A criticism of this type of flowmeter is that general anesthesia and an anticoagulant must be used because the blood vessel is cannulated. The newly developed flexible cannula now makes it possible to cannulate by use of procaine as local anesthesia, thereby eliminating one of these objections, leaving only the anticoagulant and the cannulation itself as criticism of this method of flow measurement. In favor of the vessel cannulation method it may be said that attempts at measurement from a pickup surrounding the artery by members of this group and others have entailed the difficulty of drift and extraneous pickup and changes in calibration due to variation in vessel diameter with inconstant pressure. These factors result in measurement errors of considerable magnitude. The use of an A. C. system reduces these difficulties considerably, and further work in this field also may reduce errors of potential pickup from vessel surfaces to a minimum.

This meter as described has a negligible pressure drop due to resistance, at physiologic rates of flow. The cannula may be cleaned easily following each use by means of a detergent and distilled water. It is felt that the significant modifications over previous electromagnetic flowmeters include a flexible cannula pickup with an improved ground, an electronic damping selector for critical damping and for mean flow measurement, a phase-controlling discriminator which allows accurate measurements of backflow as well as forward flow, both being linear through zero, an electronic centering device to adjust the zero point for flow measurement with minimal drift from carrier harmonics

or extraneous stray voltages, and an improved power gain enabling the system to be used with high speed recorders.

Summary

A newly modified electromagnetic blood flowmeter is described which produces a continuous permanent record of pulsatile and of mean blood flow. While the use of this meter entails some of the disadvantages inherent with cannulation, it possesses the advantages of direct flow measurement, a linear calibration both forward and backward with fidelity, accuracy, stability (drift less than 2 per cent in four hours), and ease of operation. It can measure flow in an organ where there is considerable movement of the blood vessels during flow registration, and the cannula has been found to exhibit negligible frictional resistance to fluid flow (less than 1 mm. Hg for a blood flow of 30 ml. per minute). The sensitivity is such that a flow of 30 ml. per minute will give 3 milliampere deflection from zero on a 5 milliampere Esterline-Angus Record, and a 12 mm. deflection from zero on a Brush penmotor.

Acknowledgments

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References

[1] Kolin, A.: Electromagnetic flow meter; principle of method and its application to blood flow measurements. Proc. Soc. Exper. Biol. & Med. **35:** 53, 1936.

[2] Wetterer, E.: Eine neue Methode zur Registrierung der Blutstromungsgeschwindigkeit am uneröffneten Gefäss. Ztschr. f. Biol. **98:** 26, 1937.

[3] Kolin, A.: An electromagnetic recording flowmeter. Am. J. Physiol. **119:** 355, 1937 (P).

[4] —, and Katz, L. N.: The flow of blood in the carotid artery of the dog under various circumstances, as determined with the electromagnetic flowmeter. Am. J. Physiol. **122:** 788, 1938.

[5] Jochim, K.: Some improvements on the electromagnetic flow meter. Am. J. Physiol. **126:** 547, 1939 (P).

[6] —: Electromagnetic flow meter. In Methods in Medical Research, Vol. 1. Chicago, The Year Book Publishers, 1948. P. 108.

[7] —: Circulatory system: methods; electromagnetic flowmeter. In Medical Physics, Vol. 2. Chicago, The Year Book Publishers, 1950. P. 225.

[8] Kolin, A.: An A. C. induction flowmeter for measurement of blood flow in intact blood vessels. Proc. Soc. Exper. Biol. & Med. **46:** 235, 1941.

[9] —: Alternating field induction flow meter of high sensitivity. Rev. Sc. Instruments **16:** 109, 1945.

[10] Richardson, A. W., Randall, J. E., and Hines, H. M.: A newly developed electromagnetic flow meter. J. Lab. & Clin. Med. **34:** 1706, 1949.

[11] Shipley, R. E., and Gregg, D. E.: Effect of external constriction of a blood vessel on blood flow. Am. J. Physiol. **141:** 289, 1944.

[12] —, —, and Schroeder, E. F.: An experimental study of flow patterns in various peripheral arteries. Am. J. Physiol. **138:** 718, 1943.

The Effect of Posture on Hypertension Induced by Sympathomimetic Amines in Man

By A. Littman, M.D., Ph.D., R. M. Gunnar, M.D., M.S., M.I. Grossman, M.D., Ph.D., and R. Casas, M.D.

After atropine the hypertension induced by Arterenol in man is abolished by tilting to the vertical position. This does not occur with equipressor doses of Arterenol or with atropine alone. Arterenol and atropine in combination could not be shown to have a blocking action at sympathetic ganglions in animal experiments, nor was there blockade of the carotid sinus reflex pathways. The failure to maintain Arterenol-induced hypertension after atropine was thus unexplained. Further experiments on the clinical implications of this phenomenon were performed.

IN PREVIOUS studies[1] on the effect of atropine in increasing the pressor response to Arterenol (norepinephrine) in man, we found in one subject that the headache associated with the hypertension disappeared on rising from the supine to the erect position. On determining the blood pressure after the subject stood up it was found to have fallen from 190/110 mm. Hg to 70/50. On reclining the previous high level of pressure was found to have returned.

The phenomena associated with the pressor effect of Arterenol are of interest because of the presence of this amine in the adrenal medulla[2] and in epinephrine preparations of natural origin.[3] Arterenol has also been considered by Goldenberg and co-workers[4] as a possible mediator in essential hypertension.

The present studies were performed to find out how consistently the postural depressor response occurred, and to study its mechanism.

Blood Pressure Response to Arterenol and Atropine and Tilting

Blood pressure was measured by the usual clinical auscultatory method. The heart rate was counted for one-half minute by precordial auscultation, or, if satisfactory, by palpation of the radial pulse.

Before the tilt the blood pressure and heart rate were determined at one minute intervals. When these were stable the table was tilted rapidly to the nearly vertical position. Readings were made at one-half or one minute intervals, beginning immediately on completing the tilt. After 5 to 10 minutes the table was returned to the horizontal and readings continued at one or two minute intervals for 10 minutes.

1. *Tilting from the horizontal to the nearly vertical position (about 80°) without drugs.*

This was performed on nine normal young men to ascertain that all subjects had normal postural compensatory reflexes, namely, a rise in diastolic pressure of 10 to 20 mm. Hg and either a slight rise or fall in systolic pressure with an increase in heart rate of up to 20 beats per minute.

2. *Similar tilting after atropine in doses of 1.0 to 4.0 mg. (five subjects); after 0.1 to 0.8 mg. of l-Arterenol base* (five subjects); and after various doses of both drugs given together (16 experiments on six subjects).*

The drugs were injected subcutaneously, the Arterenol being given about one hour after atropine. This order was necessary because the peak pressor effect of Arterenol by this route

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* Supplied by Dr. M. L. Tainter, Sterling-Winthrop Research Inst., Rensselaer, New York.

lasted only about 20 minutes. The various experiments were performed on separate days to avoid overlapping of drug effects. The results were as follows:

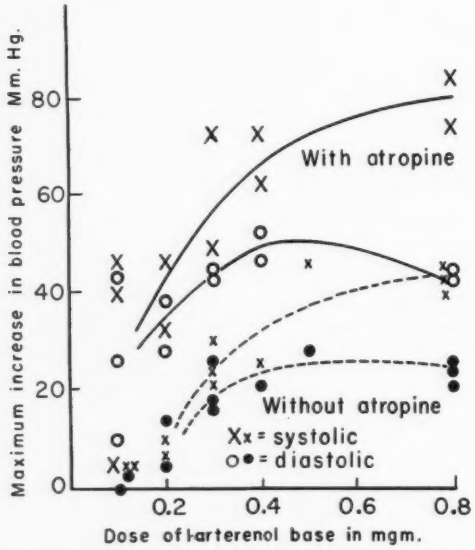

FIG. 1. Pressor response to various doses of Arterenol with and without atropine.

Atropine. In no case did hypotension occur with tilting. There was the same blood pressure response as in the control experiments, with a greater increase in heart rate.

Arterenol. The maximum pressor responses to Arterenol injected subcutaneously are shown in figure 1. Repeated doses of the same amount on different days gave closely similar responses. On tilting there was little change in blood pressure. There was no decrease in intensity of the headache in the upright position.

Arterenol after atropine. After atropinization the administration of Arterenol resulted in a hypertension of greater magnitude than that which was produced by equal doses of Arterenol alone (fig. 1). On tilting, the hypertension would give way to hypotension. Measuring from the peak pretilt pressure levels, there was a fall in systolic pressure of 20 to 150 mm. Hg and a fall in diastolic pressure of 7 to 70 mm. Hg in 10 experiments (table 1). In one experiment (experiment 1), after atropinization a small dose of Arterenol was used and no diastolic pressor response was obtained. In this experiment the subject showed a normal response to tilting, whereas in another experiment (experiment 4) with a larger amount of Arterenol (enough to produce hypertension) the same subject showed a hypotensive response to tilting. Throughout the series there was a clear correlation between the magnitude of the pressor response and the magnitude of the drop in pressure on tilting to the vertical position.

In each of the experiments in this group the headache was absent in the vertical position. The other symptoms induced by Arterenol,

TABLE 1.—*Maximum Decreases in Blood Pressure on Tilting with Hypertension Induced by Arterenol and Atropine*

Subject	Atropine mg.	l-Arterenol base mg.	Pretilt Rise in Blood Pressure (Peak, mm. Hg)		Vertical Position Maximum Drop in B.P. from Pretilt Peak		Maximum change in heart rate
			Syst.	Diast.	Syst.	Diast.	
R. C.	1.0	0.1	10	0	+8	+16	+40
L. B.	1.0	0.2	18	18	20	7	+38
L. B.	1.0	0.2	18	18	30	22	+32
R. C.	1.0	0.2	34	20	33	22	+25
L. B.	1.0	0.3	48	32	60	20	+30
M. G.	2.0	0.1	42	44	54	26	+22
A. L.	2.0	0.3	68	36	120	60	
A. L.*	2.0	0.4	74	32	45	30	−16
D. F.*	4.0	0.4	52	44	50	30	2
R. G.*	6.0	0.04	18	18	20	10	− 2
A. L.	0.5 (I.V.)	0.8	120	50	150	70	−23

* In these experiments a tilt-table was not available. The subjects stood at the bedside.

such as palpitation and dyspnea, were diminished, and the subject felt much better when upright. Promptly on return to the horizontal position the hypertension returned to the pretilt level and the symptoms also returned.

In two experiments the drop in pressure with upright position was prevented by the application of blood pressure cuffs to both thighs, and inflation to 250 mm. Hg immediately before tilting. When the cuffs were deflated while the subject was still upright there was a sudden drop to low levels. This experiment shows that intravascular pooling in the legs accounts for at least part of the drop in blood pressure.

Discussion and Studies on Animals

There are two general kinds of mechanisms which can be suggested to explain the failure to maintain blood pressure, after Arterenol and atropine, on tilting to the upright position.

First, failure of compensatory arteriolar constriction is to be considered. This could be due to a defect in either the afferent or efferent limbs of the postural vasoconstrictor reflexes.

To investigate the possibility that Arterenol and atropine might block carotid sinus reflexes the following experiments were performed: Three dogs were lightly anesthetized with sodium pentobarbital and one carotid artery was cannulated for the recording of blood pressure. Small pressor doses (10 gamma of base) of *l*-Arterenol were given intravenously. At the moment of the peak of the pressor response, the carotid which had not been cannulated was compressed low in the neck. A second peak occurred; the magnitude of the pressor response to carotid clamping was greater than that due to the dose of Arterenol used. These experiments were repeated several times after the intravenous administration of 1.0 mg. of atropine. Atropinization regularly caused slight augmentation of the pressor response to Arterenol. The response to carotid clamping after both drugs was irregularly, and at most only slightly, decreased.

The postural constrictor reflexes could be blocked at two possible sites in the efferent limb, namely, at sympathetic ganglions or at effector cells.

A study of the combined action of Arterenol and atropine on the superior cervical sympathetic ganglion of the cat was next undertaken.

In five cats under light anesthesia with sodium pentobarbital, an electrode was placed on the cervical sympathetic trunk. Movement of the nictitating membrane was recorded by means of a pulley and lever system, and blood pressure by means of a mercury manometer. A constant current was applied to the electrode with the lowest intensity which would maintain retraction of the membrane. Moderate pressor doses of Arterenol did not affect the retraction. After atropinization there was no consistent change with repeated doses of Arterenol.

There would remain a possibility that the adrenotropic receptors under the influence of Arterenol would be blocked to the neurohumoral mediators liberated by the reflex constrictor impulses. This is excluded by the regular occurrence of a pressor response to carotid sinus stimulation in the dog after Arterenol and atropine as described above.

Another possibility is that of postarteriolar vascular dilatation, as has been described for the syncope-producing effect of nitrites.[5] However, with nitrites the blood pressure is maintained in the vertical position with severe symptoms until collapse finally occurs. In our experiments the subjects felt better in the upright position, with relief of the symptoms due to the sympathetic drugs and with no tendency to collapse.

We therefore regard the postural drop in pressure after Arterenol and atropine as unexplained.

Clinical Implications; Further Experiments

Goldenberg[4] has suggested that Arterenol could be the humoral agent which mediates essential hypertension in man. On the basis of the foregoing observations, if circulating Arterenol were present in pressor amount, a postural drop in pressure could be expected after the administration of atropine. Therefore, we gave doses of 1.0 mg. of atropine to eight patients with essential hypertension. No significant decreases in blood pressure in the vertical position were found.

Another possible implication of our work is suggested by the observation of Smithwick that four of nine patients with hypertension due to pheochromocytoma had marked postural decrease in blood pressure.[6] Since both Arterenol and epinephrine are present in the blood in such patients, we studied the effect of epinephrine of natural and synthetic origin, with and without the addition of Arterenol. In 21 experiments on eight normal subjects in which hypertension was induced by the continuous intravenous administration of these drugs, there were no significant drops in blood pressure on tilting. We interpret this result to indicate that the postural hypotension which sometimes occurs in patients with pheochromocytoma is not due entirely to circulating epinephrine and/or Arterenol.

Summary and Conclusions

1. After atropinization the hypertension induced by Arterenol in human subjects is abolished by tilting to the vertical position. This phenomenon does not occur with equipressor doses of Arterenol alone or with atropine alone. The hypotension on tilting may be prevented by the inflation of blood pressure cuffs on the thighs, with a profound drop in pressure on sudden deflation. Thus, at least part of the drop in pressure appears to be due to pooling of blood in the legs.

2. Experiments on the superior cervical sympathetic ganglion in cats indicated that Arterenol and atropine together do not cause blockade at sympathetic ganglions. Further experiments on dogs showed that these drugs block neither the afferent nor the efferent limbs of the carotid sinus pressor reflex arc. Thus, our observations fail to demonstrate possible sites for interference with the mechanisms for maintenance of arteriolar constriction.

3. In our subjects the clinical observations on tilting did not resemble those in nitrite syncope, in which postarteriolar dilatation is held to be responsible.

4. The administration of atropine to patients with essential hypertension did not induce postural hypotension.

5. Pressor doses of epinephrine of natural and synthetic origin were given intravenously with and without Arterenol to normal subjects. On tilting there were no significant drops in blood pressure.

References

[1] Littman, A., Gunnar, R. M., Grossman, M. I., and Casas, R.: The electrocardiographic effect of Arterenol and isopropylarterenol in man. J. Applied Physiol. **3:** 235, 1950.

[2] Goldenberg, M., Faber, M., Alston, E. J., and Chargoff, E. C.: Evidence for the occurrence of nor-epinephrine in the adrenal medulla. Science **109:** 534, 1949.

[3] Tuller, B. F.: The separation of *l*-arterenol from natural U.S.P. epinephrine. Science **109:** 536, 1949.

[4] Goldenberg, M., Pines, K. L., Baldwin, E. de F., Greene, O. G., and Roh, C. E.: The hemodynamic response of man to nor-epinephrine and its relation to the problem of hypertension. Am. J. Med. **5:** 792, 1948.

[5] Weiss, S., Wilkins, R. W., and Haynes, F. W.: The nature of circulatory collapse induced by sodium nitrite. J. Clin. Investigation **16:** 73, 1936.

[6] Smithwick, R. H., Greer, W. E. R., Robertson, C. W., and Wilkins, R. W.: Pheochromocytoma. New England J. Med. **242:** 252, 1950.

The Q Wave in Precordial Electrocardiograms Overlying the Hypertrophied Right Ventricle: Intracavity Leads

By NOBLE O. FOWLER, JR., M.D., RICHARD N. WESTCOTT, M.D., AND RALPH C. SCOTT, M.D.

Right ventricular cavity electrocardiograms were obtained in six subjects having qR patterns in V leads made from precordial sites overlying the hypertrophied right ventricle. Four of the six, unlike control subjects, had no initial R wave in the right ventricular cavity; one had only a questionable initial R wave. Simultaneous intracavity and precordial electrocardiograms suggested that the initial Q wave over the hypertrophied right ventricle is due to abnormal depolarization of the interventricular septum, and that the large R wave over the hypertrophied right ventricle is the result of delay in activation of the free wall of that chamber.

SEMIDIRECT unipolar electrocardiographic leads (V leads) from sites on the precordium overlying the normal human right ventricle usually reveal a QRS pattern characterized by a small initial R wave and a large final S wave (rS pattern*).[1] When the right ventricle is hypertrophied, V leads obtained from the right precordium may show one of four types of QRS complex[2]: (1) the normal rS pattern; (2) right bundle branch block; (3) evidence suggesting dilatation but not hypertrophy of the right ventricle; (4) the QRS pattern which is considered diagnostic of right ventricular hypertrophy. This latter pattern, with which we are primarily concerned, is a qR pattern associated with a QRS of normal duration. Occasionally, there may be seen an rSR or qRs pattern. The Q wave in precordial leads overlying the hypertrophied right ventricle may be quite deep in proportion to the succeeding R wave, resulting in Q:R ratios ordinarily associated with myocardial infarction.[2]

Since the origin of the Q wave in electrocardiographic leads from the chest overlying the hypertrophied right ventricle is in considerable dispute[2] it was believed that electrocardiographic leads taken from the cavity of the right ventricle in subjects showing such a Q wave might shed light on the mechanism of its production.

MATERIAL

Six patients having a qR or qRs pattern in electrocardiographic leads overlying the right ventricle were obtained from the medical wards of the Cincinnati General Hospital and from the medical wards of the Veterans Hospital, Dayton, Ohio. All patients had roentgenographic evidence of right ventricular hypertrophy.

As controls, right ventricular cavity leads were obtained in three subjects who had rS patterns in precordial leads overlying the right ventricle. Two of these subjects had emphysema of the lungs.

METHOD

Cardiac catheterization was performed by methods described previously,[3] using catheters containing a wire electrode buried in their walls. In all instances the position of catheter tip was verified both by fluoroscopy and by viewing the pressure curve on an oscilloscopic viewing screen before taking the intracavity electrocardiograms. Simultaneous precordial and intracavity electrocardiograms were obtained with the Technicon Triagram electrocardiograph. Electrocardiograms were recorded at two speeds: slow speed at 25 mm. per second and fast speed at 50 mm. per second. Nonsimultaneous electrocardiograms were obtained with the Sanborn Visocardiette. In some instances the precordial and intracavity electrocardiograms were timed for superimposition by a simultaneous recording of the right ventricular pressure curve. Intracardiac leads were recorded at one-tenth to one-half normal sensitivity.

Intracardiac pressures were recorded by means of

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* In discussing the QRS complex of the electrocardiogram, small letters will be used to designate relatively small deflections; capital letters will be used to designate large deflections.

the five-channel Hathaway pressure recording apparatus. Blood samples, collected under oil and stored in ice over mercury, were analyzed for oxygen and carbon dioxide in the Van Slyke manometric apparatus. Duplicate samples were required to check within 0.2 volume per 100 cc.

the intrinsicoid deflection is delayed, the R is prominent, and the S is small.

Intracavity leads (fig. 2) were taken from the pulmonary conus, midzone of the right ventricle, low in the right ventricle, right ventricular side of the tricuspid valve and low in the right atrium. In

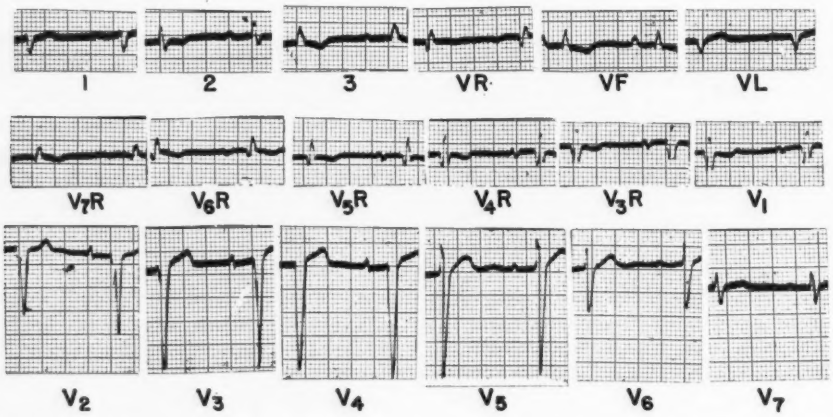

FIG. 1. Case D. H. Standard and unipolar electrocardiographic leads: unipolar precordial leads. The limb leads show right axis deviation. Leads V_{3R} through V_{7R} show the qR or qRs pattern indicative of right ventricular hypertrophy.

RESULTS

Case Reports

D. H., a 61 year old white man, had pulmonary emphysema confirmed by spirometry, chronic cor pulmonale, and secondary polycythemia. An angiocardiogram revealed right ventricular hypertrophy. Cardiac catheterization performed May 26, 1950 revealed a pulmonary artery pressure of 75/25 mm. Hg. Arterial oxygen saturation was 68.27 per cent of capacity. Hemoglobin was 17.45 Gm. per 100 cc. of blood (Van Slyke oxygen capacity method). Arterial carbon dioxide content was 66.84 volumes per 100 cc. of blood. The arterial hypoxemia and hypercapnia were considered characteristic of severe pulmonary emphysema. The pulmonary arterial hypertension was in keeping with the impression of cor pulmonale.

The standard lead electrocardiogram, together with unipolar extremity leads and unipolar precordial leads, is shown in figure 1. The standard leads show right axis deviation. Lead aVR shows a qR complex, consistent with but not diagnostic of right ventricular hypertrophy. Since the QRS pattern of lead V_1 was not typical of right ventricular hypertrophy, leads V_{6R}, V_{5R}, V_{4R} and V_{3R} were taken. These V leads all showed the classic qR or qRs pattern of right ventricular hypertrophy. In the leads V_{7R} through V_1, the qRs pattern differs from that seen in septal infarction in the fact that here

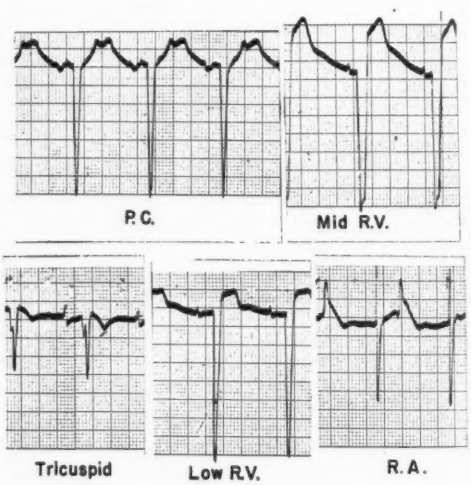

FIG. 2. Case D. H. Unipolar intracavity electrocardiographic leads. Leads show absence of an initial R wave in the right ventricle.

none of these areas was a definite initial R wave seen in the QRS complex.

C. B., a 56 year old white man, had pulmonary emphysema, cor pulmonale, and congestive heart failure. Hematocrit was 59.

On Dec. 22, 1950, cardiac catheterization was performed. Pulmonary artery pressure was 90/45 mm. Hg. Right ventricular pressure was 80/15–7 mm. Hg. Systemic arterial oxygen saturation was 51 31 per cent of capacity. Systemic arterial carbon dioxide content was 65.69 volumes per 100 cc. of blood. Hemoglobin was 16.87 (Van Slyke oxygen capacity method).

The intracardiac electrocardiographic leads and standard leads, unipolar extremity leads and unipolar precordial leads obtained at the time of catheterization are reproduced in figures 3 and 4. The standard leads show right axis deviation and deep Q waves in leads II and III. There is a definite Q wave in leads V_{4R}, V_{3R}, and V_1; all show the QRS complex characteristic of right ventricular hypertrophy. It was felt that the patient possibly had healed posterior myocardial infarction in addition because of the large Q wave lead in V_F; however, the probability that this Q wave was referred from the posterior transitional zone between right and left ventricles could not be excluded. Simultaneous precordial and intracavity electrocardiograms (fig. 4) revealed that the Q wave in lead V_{3R} was simultaneous in onset with the initial downward deflection in tracings made from the right ventricular cavity. In no part of the right ventricular cavity was the normal rS pattern obtained. Since there was no electrocardiographic evidence of massive septal infarction, it was felt that the possible old posterior myocardial infarct played no role in the absence of an R wave in the right ventricular cavity leads.

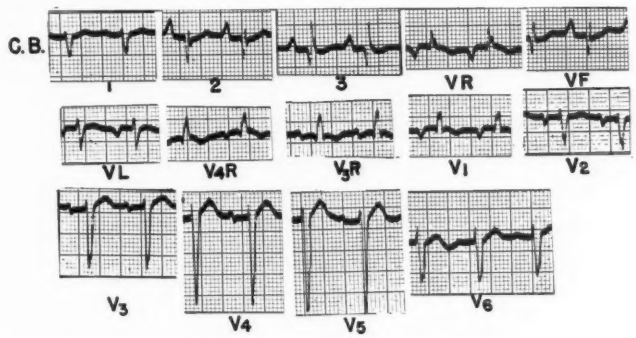

FIG. 3. Case C. B. Standard and unipolar electrocardiographic limb leads: unipolar precordial leads. Standard leads show right axis deviation and a deep Q wave in leads II and III. Leads V_{4R}, V_{3R} and V_1 show the qR or qRs pattern characteristic of right ventricular hypertrophy.

R. P., a 62 year old Negro man, had bronchiectasis, pulmonary emphysema, cor pulmonale, and congestive heart failure.

Cardiac catheterization was performed on Jan. 5, 1951. Brachial artery blood showed oxygen saturation 76.9 per cent of capacity and a carbon dioxide content of 64.22 volumes per 100 cc. of blood. Hemoglobin (Van Slyke) was 14.38 Gm. per 100 cc. Right ventricular pressure was 54/7 mm. Hg.

The standard electrocardiographic leads, unipolar extremity leads, and unipolar precordial leads obtained at the time of cardiac catheterization are reproduced in figures 5 and 6.

The standard leads show right axis deviation. Lead V_{4R} shows a qR pattern with the QRS complex of normal duration. There is a small initial R wave in leads V_{3R} and V_1. Lead V_6 (fig. 6) contains a rather wide S wave in the QRS complex. These findings are considered indicative of right ventricular hypertrophy. Intracavity leads from the apex of the right ventricle revealed a QS pattern.

J. S. was a 54 year old white man suffering from pulmonary emphysema and cor pulmonale without congestive heart failure.

Cardiac catheterization was performed Oct. 27 1950. Pulmonary artery pressure was 55/32 mm. Hg. Right ventricular pressure was 56/2.5 mm. Hg. The systemic arterial blood was 81.3 per cent saturated with oxygen and contained 52.09 volumes of carbon dioxide per 100 cc. of blood. Hemoglobin (Van Slyke oxygen capacity method) was 14.74 Gm. per 100 cc. of blood.

Standard and unipolar limb leads and unipolar precordial lead electrocardiograms were made. The standard leads revealed right axis deviation. There was a large Q wave in lead III and in lead V_F; this was thought to be referred from the Q wave over the right precordium. Leads V_{5R} and V_{4R} revealed the QRS pattern characteristic of right ventricular hypertrophy. Intracavity leads within the right ventricle taken at one-half and one-third normal sensitivity revealed only a questionable R wave and a large S wave.

Patient E. S. was a 54 year old Negro man who had cor pulmonale in congestive failure. Venous

blood carbon dioxide combining power was 64 volumes per 100 cc.

Cardiac catheterization was performed Aug. 18, 1950. The pulmonary artery pressure was found to be 72/30 mm. Hg. Right ventricular pressure was 60/9 mm. Hg.

Intracavity electrocardiograms were taken along with the standard leads, unipolar extremity leads, and unipolar precordial leads. The standard leads showed right axis deviation. Leads V_{3R}, V_{4R}, and from near the apex of the right ventricle. However, it was believed that the initial deflection in the leads from the mid-right ventricle and apex of the right ventricle is a Q wave; that in the pulmonary conus was definitely a Q wave. An apparent minute initial R wave in the right atrial and tricuspid lead may have come from the left ventricular cavity via the mitral orifice and left atrium. An initial R wave in the pulmonary artery lead probably came from the left ventricular cavity via the aorta.

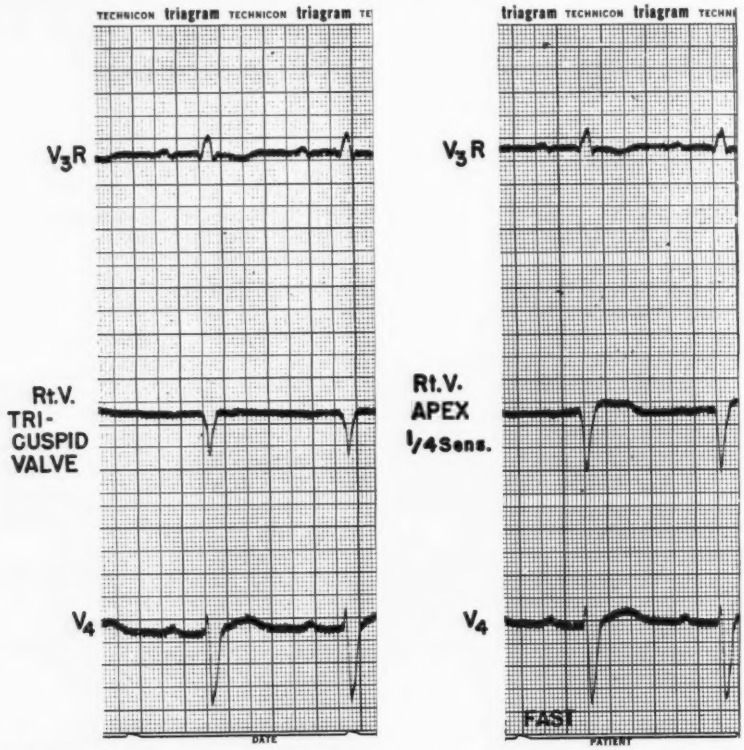

FIG. 4. Case C. B. Simultaneous precordial and intracavity electrocardiogram. Shows the absence of initial R waves within the right ventricular cavity. The downstroke in the cavity lead is simultaneous with the onset of the Q wave in lead V_{3R}.

V_{5R} demonstrated the characteristic QRS pattern of right ventricular hypertrophy. Intracavity leads taken at approximately one-half normal sensitivity revealed no initial R wave in the region of the pulmonary conus or tricuspid valve of the right ventricle.* Unfortunately the onset of the QRS complex was partially obscured by an artefact in leads obtained from the middle of the right ventricle and

R. T., a 22 year old white man, had uncomplicated pulmonic stenosis. Cardiac catheterization was performed Dec. 19, 1950. As the catheter was advanced through the superior vena cava, right atrium, right ventricle, and pulmonary artery, in no instance was there a rise of even 0.1 volume per 100 cc. in oxygen content, thus excluding a left to right intracardiac shunt. Systemic arterial oxygen saturation was 96.15 per cent of capacity, thus militating against a right to left intracardiac shunt. Pressure in the pulmonary artery was 18/10 mm. Hg. and in the right ventricle 165/7 mm. Hg.

Standard electrocardiographic leads, unipolar

* We are indebted to Dr. Gordon B. Myers, Professor of Medicine, Wayne University, for the following analysis of the electrocardiograms of this patient.

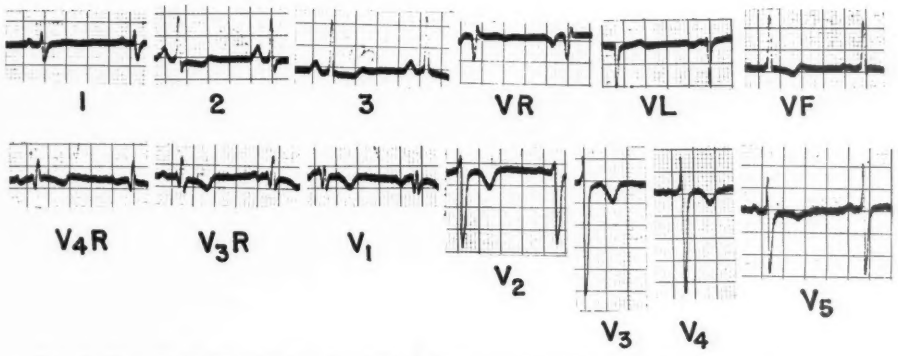

FIG. 5. Case R. P. Standard and unipolar electrocardiographic limb leads: unipolar precordial leads. The standard leads show right axis deviation. Lead V_{1R} shows the qR pattern diagnostic of right ventricular hypertrophy.

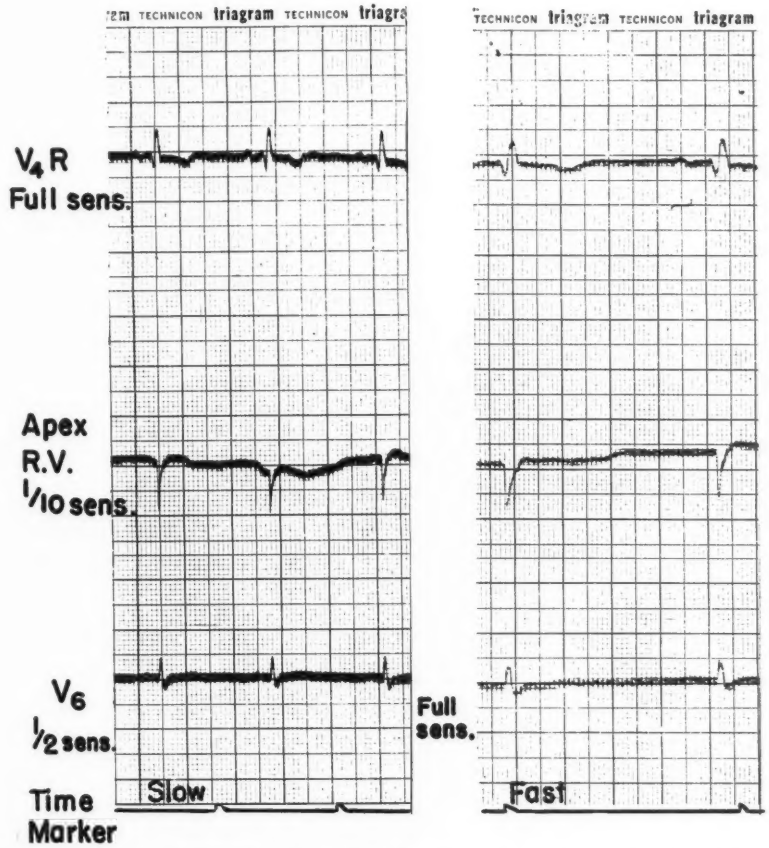

FIG. 6. Case R. P. Simultaneous precordial and intracavity electrocardiogram. Shows the absence of an initial R wave in the right ventricular cavity lead.

limb and precordial leads and simultaneous intracavity and precordial leads were made. The standard leads showed marked right axis deviation. Leads V_2, V_{3R}, V_{4R}, and V_{5R} each revealed the characteristic QRS pattern of right ventricular hypertrophy. Intracavity leads obtained from the midportion of the right ventricle at one-fifth normal sensitivity demonstrated a small initial R wave occurring simultaneously with Q wave in leads V_{4R} and V_{5R}.

Control Studies

In each of three control subjects intracavity leads from the right ventricle revealed an rS pattern. All controls had rS patterns in semidirect unipolar leads from the precordium over the right ventricle. Two control subjects had emphysema; the other had no evidence of heart disease.

Discussion

Following the investigations of Hecht[4] and others, Levine[5] found an rS pattern in 24 of 27 normal subjects in electrocardiograms taken from the right ventricular cavity. This normal initial positivity, found also in our control subjects, is interpreted as indicating earlier activation of the left side of the interventricular septum in the normal course of ventricular depolarization.[1]

The cause of the initial Q wave in V leads over the hypertrophied right ventricle is in dispute. One group of investigators has stated that the qR complex in right precordial leads in right ventricular enlargement is due to extreme clockwise rotation of the heart so that the electrode in the V_1 position is facing the posterobasal portion of the left ventricle.[6–9] Kert and Hoobler[10] have suggested that the initial Q wave over the right precordium in the aforementioned condition may be due to activation of some part of the left ventricle prior to septal depolarization. Sodi-Pallares believes that the initial Q wave in right ventricular hypertrophy is the result of transmission of negative potentials in the right auricle to the right side of the precordium.[11] Myers[2] believes that the initial Q wave over the right ventricle in right ventricular hypertrophy may be due to one of two factors: the interventricular septum may be activated from right to left instead of from left to right as is thought to occur normally; or, the septum may be activated normally from left to right, but the resulting initial R wave of the right ventricular cavity may be so small that is is not transmitted to the right precordium, where an inital Q wave may appear as the result.

Schlesinger[12] and co-workers studied five cases of right ventricular hypertrophy by means of right ventricular cavity leads; one of their cases had a qR complex in lead V_1. This case also had an initial Q wave in the right ventricular cavity electrocardiogram. Kert and Hoobler[10] also found an initial Q wave in the right ventricular cavity lead of a case of right ventricular hypertrophy having a qR complex in lead V_1.

In our series we have studied six cases of right ventricular hypertrophy having a qR complex in V leads over the right precordium. Only one of these had a definite initial R wave in the right ventricular cavity. One other had a questionable initial R wave in the right ventricular cavity, certainly indicating weakness of septal forces. In four cases there was a definite QS pattern in the right ventricular cavity; in two of these, simultaneous records were obtained demonstrating the onset of the QS pattern in the right ventricular cavity to be simultaneous with the beginning of the Q wave in semidirect leads over the right ventricle.

The evidence in the cases we have studied is in accordance with the theories of Myers.[13] In the cases having a QS pattern in the right ventricular cavity leads, one would assume that the interventricular septum is being activated either from right to left, or simultaneously on the two sides. Unfortunately, we do not have intracavity leads from the left ventricle, which would serve to show conclusively whether the septum were activated from right to left initially. Wilson[14] has stated that the initial Q waves in ventricular hypertrophy may be due to a decreased density of the junctions between Purkinje fibers and ordinary heart muscle in certain areas as a result of dilatation of the chamber chiefly affected. In the one and possibly two cases in our group showing a small initial R wave in the right ventricular cavity leads, we believe that left to right septal depolarization has been interfered with, but to a

lesser degree, resulting in a small initial R wave in the right ventricular cavity which is lost in transmission to the V leads over the right precordium.

The mechanism producing the large R wave of the qR complex in right ventricular hypertrophy is also of interest. Kossmann[6] has concluded that this R wave is produced by activation of the free wall of the left ventricle from his finding that the nadir of Q and the peak of R occurred simultaneously in V leads over the posterior left chest and in lead V_1 in subjects with right ventricular hypertrophy. McGregor[9] supported Kossmann's concept by demonstrating rS patterns in direct right ventricular epicardial leads taken at operation in 10 cases of tetralogy of Fallot.

In this connection, it is of interest to examine the electrocardiogram of subject R. R. (fig. 6), showing leads V_{4R}, lead V_6, and the right ventricular cavity lead recorded simultaneously. In comparing the right ventricular cavity lead with lead V_6, one notes that the nadir of the S wave in the former occurs simultaneously with the peak of R in the latter, indicating that both are produced by the arrival of the force of excitation at the epicardial surface of the left ventricle. The nadir of S in V_6 occurs simultaneously with the peak of R in V_{4R}, suggesting that both are produced by activation of the free wall of the right ventricle. In comparing the time of onset of the peak of R in V_{4R} with the time of occurrence of the nadir of S in the right ventricular cavity lead in figure 6, one notes that the peak of R in V_{4R} occurs 0.03 second later than the nadir of S in the cavity lead. In figure 4, the record of subject C. B. shows the peak of R in lead V_{3R} to occur 0.04 second later than the nadir of S in the lead taken from the right ventricular cavity near the apex. The occurrence of the peak of R in leads over the right ventricle later than the arrival of the force of excitation at the free wall of the left ventricle would seem to indicate that the R wave in leads over the right ventricle is produced by the activation of the right ventricular wall, since there is no R wave of comparable magnitude in the leads obtained from the right ventricular cavity.

Summary and Conclusions

Intracavity electrocardiograms were obtained from the right ventricle in six cases of right ventricular hypertrophy having qR complexes in the V leads made from sites over the right precordium, and in three subjects without right ventricular hypertrophy having rS complexes in the V leads obtained from sites over the right ventricle. In four of the subjects with right ventricular hypertrophy, the right ventricular cavity electrocardiogram showed no initial R wave; in one the R wave was questionable; in one there was a definite initial R wave in the right ventricular cavity leads. The control subjects each showed a definite initial R wave in the right ventricular cavity leads.

It is concluded that the normal early left to right depolarization of the interventricular septum is often interfered with in right ventricular hypertrophy to the extent that the normal initial R wave of the intraventricular QRS electrocardiogram is not produced or is diminished in amplitude. The absence or diminution of this R wave may be responsible for the initial Q wave in V leads obtained from precordial sites over the right ventricle in hypertrophy of that chamber.

It is also concluded that the delayed R wave of the qR electrocardiographic pattern in the V leads obtained from precordial sites over the hypertrophied right ventricle is probably produced by activation of the free wall of the right ventricle.

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REFERENCES

[1] Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Menezes de Oliveira, R., Scarsi, R., and Barker, P. S.: The precordial electrocardiogram. Am. Heart J. **27:** 19, 1944.

[2] Myers, G. B.: QRS-T patterns in multiple precordial leads that may be mistaken for myo-

cardial infarction. II. Right ventricular hypertrophy and dilatation. Circulation **1:** 860, 1950.

[3] Fowler, N. O., Westcott, R. N., Scott, R. C., Hauenstein, V. D., and McGuire, J.: Observations on autonomic participation in pulmonary arteriolar resistance in man. J. Clin. Investigation **29:** 1387, 1950.

[4] Hecht, H. H.: Potential variations of the right auricular and ventricular cavities in man. Am. Heart. J. **32:** 39, 1946.

[5] Levine, H. D., Hellems, H. K., Dexter, L., and Tucker, A. S.: Studies in intracardiac electrography in man. Am. Heart J. **37:** 64, 1949.

[6] Kossmann, C. E., Berger, A. R., Brumlík, J., and Briller, S. A.: An analysis of the causes of right axis deviation based partly on endocardial potentials of the hypertrophied right ventricle. Am. Heart J. **35:** 309, 1948.

[7] Wolff, L.: Electrocardiography. Philadelphia and London, W. B. Saunders, 1950. P. 187.

[8] Goldberger, E.: Unipolar Lead Electrocardiography. Philadelphia, Lea and Febiger, 1949. P. 392.

[9] McGregor, M.: The genesis of the electrocardiogram of right ventricular hypertrophy. Brit. Heart J. **12:** 351, 1950.

[10] Kert, M. J., and Hoobler, S. W.: Observations on the potential variations of the cavities of the right side of the human heart. Am. Heart J. **38:** 97, 1949.

[11] Sodi-Pallares, D., Thomsen, P., Soberón, J., Fishleder, B. L., Estandía, A., and Barbato, E.: El electrocardiograma intracavitario humano. México, Instituto Nacional de Cardiología, 1948. P. 110.

[12] Schlesinger, P., Benchimol, A. B., and Cotrim, M. R.: Intracavity and esophageal potentials in right ventricular hypertrophy. Am. Heart J. **37:** 1110, 1949.

[13] Myers, G. B.: The form of the QRS complex in the normal precordial electrocardiogram and in ventricular hypertrophy. Am. Heart J. **39:** 637, 1950.

[14] Wilson, F. N., Rosenbaum, F. F., and Johnston, F. D.: Interpretation of the ventricular complex of the electrocardiogram. Advances in Internal Medicine, Vol. II. New York, Interscience Publishers, 1947. P. 642.

Rupture of an Aortic Aneurysm into the Pulmonary Artery

A Case Report

By Curtis H. Carter, M.D., William N. Agostas, M.D., and V. P. Sydenstricker, M.D.

A case report of rupture of an aortic aneurysm with antemortem diagnosis and a brief review of the common clinical findings in this syndrome are presented. The case reported was studied by cardiac catheterization which, it is felt, confirmed the clinical diagnosis. Postmortem findings are given and a drawing and photograph of the specimen is shown.

THE SYNDROME of rupture of an aortic aneurysm into the pulmonary artery, though uncommon, has been reported with sufficient frequency as to constitute a fairly definite clinical entity. A review of the literature in 1943 by Nicholson[1] revealed 81 case reports, to which he added two of his own. Ninety-one per cent of these cases occurred in males. In 85 per cent of the cases the location of the aneurysm was in the ascending aorta. It was noted that if death occurred soon after rupture, the tear was usually irregular in shape; however, if erosion was slow the aperture was usually smooth and oval. The characteristic murmur noted in most cases was a continuous one with systolic accentuation, though in some of the cases the murmur was noted as being systolic only. There was a thrill in 68 per cent of the cases, and in the majority the timing was either systolic or continuous. A collapsing pulse was demonstrated in more than half of the cases, and cyanosis or pallor was noted in 66 per cent. Edema of the extremities, dyspnea and cough were prominent symptoms. The x-ray picture usually revealed an aneurysmal sac extending to the left of the sternum with an associated dilatation of the pulmonary conus. Slight to marked cardiac enlargement was usually described. Electrocardiograms reported in six cases did not appear to be specific.

According to Nicholson,[1] the typical clinical picture consists of a sudden onset of severe precordial pain and dyspnea after strain. Edema develops rapidly and cyanosis or pallor is often seen. At the onset euphoria and oliguria may be present. The extremities are frequently cold to the touch. The patient develops paroxysms of coughing with expectoration; palpitation may be a prominent feature. On examination, the patient usually appears acutely ill and exhibits moderate dyspnea. Moderate pallor or cyanosis and edema are usually observed. An intense purring thrill, either systolic, diastolic or both is usually palpable over the precordium at the pulmonic area. On auscultation a typical crescendo-decrescendo harsh murmur can usually be heard. The usual signs of aortic regurgitation are present.

It was noted by Nicholson[1] that only four of the cases reviewed had been diagnosed ante mortem; however, he presented two case reports of his own wherein the diagnosis had been made before death.

In 1950, Klein and Porter[2] presented a case report wherein the patient survived 14 months after onset. Of special interest in this case report were the catheterization studies carried out during the hospitalization of the patient. In summary, the results of these studies revealed an increased pressure in the right ventricle and pulmonary artery and increased oxygen saturation of blood in the pulmonary artery. Catheterization in this case was considered to be an important diagnostic aid. A correct antemortem clinical diagnosis was made in this case which was definitely confirmed by catheterization studies.

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In view of the infrequent antemortem diagnosis made in these cases and in view of the valuable information obtained by heart catheterization, it was felt that a case report wherein a correct antemortem diagnosis had been made would be of considerable interest.

Case Report

J. W., a 28 year old Negro man, was admitted to the University Hospital on Oct. 25, 1949, with the chief complaint of shortness of breath and swelling of the face, feet and ankles.

History of present illness revealed that the patient had to stop work about five weeks before admission because of a cough and a constant choking sensation. Dyspnea increased, and two weeks prior to admission the patient noted onset of swelling of the face, abdomen and lower extremities. On this same date he noted that the shortness of breath had increased, and he began to experience orthopnea at night. Because of increasing dyspnea the patient was forced to go to bed about one week prior to admission.

Past History. In 1936 the patient had had lymphogranuloma venereum. For the past five years the patient noted that he seemed to keep a cold most of the time, usually accompanied by an annoying cough. A positive serologic reaction was noted in 1943 and was followed by two years of antisyphilitic therapy with bismuth and arsenic preparations. Repeat serologic test in 1945 was again positive and the patient received six additional months of antisyphilitic therapy. About one year prior to admission he developed a sudden pain in his left chest with radiation to the posterior thorax. At that time he had the sensation that something had "snapped" in his chest. Following the attack he remained in bed for four days and experienced a suffocating sensation most of the time. During this period he also noted marked palpitation and afterwards experienced difficulty sleeping because of frequent sensations of suffocating after going to bed.

On admission examination revealed a well developed and well nourished Negro man appearing acutely ill and exhibiting orthopnea. The blood pressure was 145/60. The pulse rate was 90, and of Corrigan type. There was obvious facial and periorbital edema; the neck veins were distended. The left cardiac border was at the anterior axillary line, the right border along the right margin of the sternum. A systolic thrill was palpable in the third left intercostal space 4 cm. from the midsternal line. In this same area there was a loud, harsh, blowing systolic murmur and a fainter diastolic murmur. The murmur was of the crescendo-decrescendo type. The murmur tended to diminish in intensity if auscultation was performed at any area away from the third left intercostal space. Medium moist rales were noted at both bases. The liver was enlarged three fingerbreadths below the right costal margin, and a hepatojugular reflex was present. Moderate ascites was also present. Three plus presacral edema and 3 plus edema of the lower extremities were present.

The red blood cells numbered 4,660,000; the white blood cells, 5,300. Hemoglobin was 14 Gm. Neutrophils were 61 per cent, lymphocytes 30 per cent, monocytes 4 per cent, eosinophils 5 per cent. Corrected sedimentation rate was 14 mm. in one hour. Preparations for sickling were negative. Nonprotein nitrogen was 29 mg. per 100 cc., sugar 105 mg. per 100 cc. and chlorides 460 mg. per 100 cc. The blood Kahn test was negative. Total proteins were 6.15 Gm. per 100 cc.; albumin 3.3 Gm. per 100 cc., globulin 2.85 Gm. per 100 cc. Spinal fluid examination revealed total protein of 32 mg. per 100 cc. with a normal colloidal gold curve. Quantitative Wasserman on spinal fluid was negative for 0.1, 0.25, and 0.5 cc. of fluid, but was positive for 1 cc. of fluid. On admission the electrocardiogram revealed sinus tachycardia with incomplete right bundle branch block. Urinalysis revealed a 2 plus albuminuria with a specific gravity of 1.010. X-ray of the chest (fig. 1) revealed considerable cardiac enlargement with pulmonary congestion bilaterally. Unusual enlargement of the pulmonary conus area was noted.

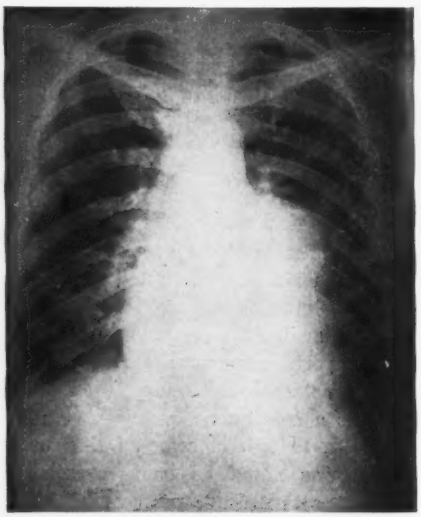

Fig. 1. X-ray film of the patient's chest.

The admission clinical diagnosis was (1) syphilitic heart disease with syphilitic aortitis and aortic insufficiency; (2) congestive heart failure; (3) left hydrothorax.

On October 26 venous pressure was 300 mm. H_2O. The circulation time, arm to tongue, with Decholin was 25 seconds. The patient was started on digitalis

and diuretics in addition to oxygen and a low sodium diet. Some improvement was obtained; however, the patient continued to have medium rales at both bases and to experience moderate dyspnea and at times orthopnea. It was the impression of two observers, after fluoroscopy of the chest, that the diagnosis was probably patent ductus arteriosus. However, after a review of the history and findings, it was the impression of one of the authors (V. P. S.) that the diagnosis in this case was rupture of a syphilitic aortic aneurysm into the pulmonary artery. In view of this impression the patient was scheduled for cardiac catheterization, and on Nov. 8, 1949, cardiac catheterization was performed by Doctors R. G. Ellison, W. F. Hamilton, Jr. and W. F. Hamilton, Sr. The results are summarized in table 1. The findings revealed an elevated pulmonary artery pressure and a high oxygen saturation of blood from the pulmonary artery. These results indicated a definite left to right shunt which could be explained only on the basis of some lesion similar to a patent ductus arteriosus.

TABLE 1.—*Physiologic Observations Obtained from Catheterization Studies*

Position Catheter	Oxygen Content	% Saturated	Pressure
1. P.A. (right)	14.79 Vol. %	84	40–50 / 20–40
2. R.V.	11.6	66	40–60 / 0–10
3. R.A.	12.16	69	10–15
4. B.A.	17.37	99	
5. Capacity	17.53		

$$\text{Pulmonary Flow} = \frac{353}{173.7-147.9} = \frac{353}{25.8} = 13.68 \text{ L./min.}$$

$$\text{Peripheral Flow} = \frac{353}{173.7-116} = \frac{353}{57.7} = 6.11 \text{ L./min.}$$

Shunt (Left to right) = 13.68 − 6.11 = 7.57 L./min.

P.A.—Pulmonary artery.
R.V.—Right ventricle.
R.A.—Right auricle.
B.A.—Brachial artery.
Oxygen consumption = 353 cc./min.

After catheterization the patient's blood pressure was 100/50, and for several hours the diastolic component of the previously described murmur was inaudible. However, the next day both systolic and diastolic murmurs were again audible, as originally described. The clinical diagnoses were changed to syphilitic aneurysm with rupture into pulmonary artery, congestive heart failure and left hydrothorax. The patient's course was progressively downhill with gradual increase in the size of the heart, though there was some diminution in edema. During this period the patient was able to be partially ambulatory, and on Nov. 18, 1949 he left the hospital against medical advice. The patient expired at his home on Nov. 25, 1949.

Postmortem Examination. On Nov. 29, 1949, an autopsy was performed by Dr. C. M. Phillips, Jr. The final anatomic diagnoses were (1) syphilitic aortitis, (2) aneurysm of aorta with rupture into pulmonary artery, (3) myocardial hypertrophy and dilatation, (4) aortic insufficiency, (5) chronic passive congestion of lungs and viscera, (6) early bronchopneumonia, (7) chronic pericarditis. The heart (fig. 2) weighed 575 Gm. The right ventricular musculature measured 0.7 cm., and the left ventricular musculature measured 1.9 cm. Considerable hypertrophy of the right auricle and ventricle with much dilatation of the chambers was present. There was moderate hypertrophy and dilatation of the left ventricle. There was fibrosis of the aorta and margins of the aortic valves. The septal cusp of the aortic valve was rather tense and flattened against the wall of the corresponding sinus. There was a circumscribed area of sclerosis with bulging involving the anterior surface of the proximal portion of the aorta for a distance of 6 cm. and measuring 4.5 cm. in width. There was longitudinal wrinkling of the

Fig. 2. Photograph of heart showing section through aneurysm of aorta revealing pulmonary artery.

wall and the proximal portion of this area. This area bulged some 1 cm. outside the diameter of the proximal aorta. Near the center of this bulging area and 1.5 cm. above the aortic valve there was a defect in the wall of the aorta 2 cm. in diameter (fig. 3). This defect communicated with a saccular aneurysm 7.5 cm. in diameter. The aneurysm projected anteriorly and into the left anterior pleural cavity displacing the pulmonary artery laterally to the left and posteriorly. The wall of the aneurysm varied from 0.3 to 2.0 cm. in thickness, and included a laminated blood clot on the anterior side. In the posterolateral portion of the aneurysm was a slit-like defect which measured 1.5 cm. long which communicated with the pulmonary artery 0.8 cm. above the pulmonary valve.

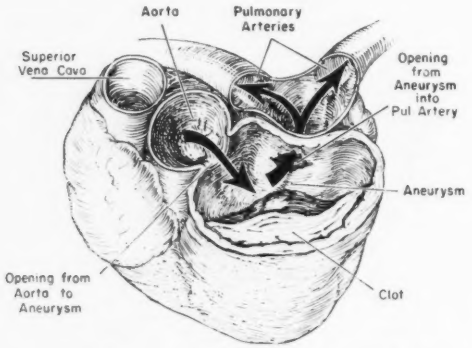

FIG. 3. Drawing of specimen shown in fig. 2.

Microscopic examination of a section from the septum of the left ventricle, including the aortic valve and the wall of the aneurysm, revealed moderate myocardial hypertrophy with scarring at the base of the aortic valve. Dense hyalinized fibrous tissue encroached upon the myocardium with vascularization of this area. Adjacent to this area was the dense, hyalinized, partially calcified, fibrous wall of the aneurysm. A few foci of plasma cells and lymphocytes were noted in the scarred area with vascularization and focal scarring of the included aorta. Examination of a section from the ascending aorta revealed patchy fibrosis of the muscularis which extended to the inner third of some areas, and was associated with vascularization of the muscularis. Occasional foci of lymphocytic and plasma cell infiltrations of the adventitia and endarteritis obliterans of the adventitia were noted. There was hyalinization and thickening of the intima. The section from the ruptured area of the aneurysm into the pulmonary artery revealed vascularization and hyalinization of the pulmonary artery at this point with perivascular and lymphocytic and plasma cell infiltration. The wall of the aneurysm was composed of dense hyalinized fibrous tissue.

COMMENT AND DISCUSSION

The history in this case leaves some doubt as to the exact time of onset of the rupture; however, the history of sudden onset of pain in the left chest one year prior to admission might indicate that partial rupture occurred at that time. The previous history of a cough for about five years would suggest the development of symptoms referable to an aneurysm. According to the patient's history, severe symptoms relative to failure did not begin until about five weeks prior to admission, and it is possible that the defect became larger at that time. On the other hand, the history could be interpreted to indicate that the actual rupture occurred five weeks prior to admission. With the pathologic changes of the aortic cusps, noted at autopsy, it is entirely possible that the patient had had an aortic insufficiency for several years. This feature may have contributed to the etiology of the left ventricular hypertrophy.

Fluoroscopy and x-ray films failed to reveal an aneurysm of the aorta, and this, coupled with the prominent pulmonary conus and general cardiac enlargement, favored the diagnosis of patent ductus arteriosus. However, a review of the patient's history, added to the findings of cardiac catheterization, pointed the way to a correct diagnosis in this case. As noted in table 1, results of cardiac catheterization revealed a shunt of 7.57 liters per minute. This may not represent the true size of the shunt, since the sample was taken from the right pulmonary artery. The oxygen consumption was high but the patient was not basal. The peripheral flow was a little low for the oxygen consumption as indicated by the high arteriovenous difference. The catheterization studies revealed a marked increase of the oxygen saturation of the pulmonary arterial blood and a significant increase of the pressure within the pulmonary artery.

As pointed out by Klein and Porter,[2] three factors may result in the elevation of pulmonary arterial pressure; these are (1) compression of the pulmonary artery by the aneurysm, (2) the obstructive "watergate" effect, and (3) increased volume of blood in the pulmonary circuit.

In 1942, Porter[3] presented three case reports and an excellent summary of the symptoms and signs usually noted in this syndrome. He pointed out that a preponderance of right ventricular failure usually appeared soon after onset and that the signs of pulmonary stasis were usually slight when compared with the amount of dyspnea present. He noted that the cardiac enlargement was usually not of the aortic type and that the electrocardiogram may go on to right axis deviation when this is not evident at the onset. He felt that the marked dyspnea was secondary to an increased Hering-Breuer reflex which was the result of marked pulmonary engorgement and not secondary to left ventricular failure. Right ventricular strain is usually prominent in these cases and can result from compression of the pulmonary artery by the aneurysm or from increased pressure within the pulmonary artery as a result of the communication between the aneurysm and the pulmonary artery.

On Nov. 4, 1949, a repeat electrocardiogram on this patient revealed a tendency to right axis deviation and on Nov. 15, 1949, the electrocardiogram revealed definite right axis deviation. This finding is consistent with the findings noted in most of the previously reported cases. However, in the case report by Klein and Porter,[2] a normal axis was present.

Summary and Conclusions

1. A patient with syphilitic aneurysm of the ascending aorta with rupture into the pulmonary artery is presented.

2. Cardiac catheterization was performed with results indicating a left to right shunt in blood flow. This finding coupled with a detailed history reveals the usefulness of cardiac catheterization as a valuable adjunctive tool in the diagnosis of the above syndrome.

REFERENCES

[1] Nicholson, R. E.: Syndrome of rupture of aortic aneurysm into the pulmonary artery: review of the literature with report of two cases. Ann. Int. Med. **19:** 286, 1943.

[2] Klein, A., and Porter W. B.: Syphilitic aneurysm of the aorta with rupture into the pulmonary artery. Am. Heart J. **39:** 465, 1950.

[3] Porter, W. B.: The syndrome of rupture of an aortic aneurysm into the pulmonary artery. Am. Heart J. **23:** 468, 1942.

CLINICAL PROGRESS

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Needless Restrictions Imposed on Cardiac Patients

By ROBERT L. LEVY, M.D.

MANY physicians appear to be too strict and particular in the rules of diet and regimen, which they deliver as proper to be observed by all who are solicitous either to preserve or recover their health. The too anxious attention to these rules hath often hurt those who are well, and added unnecessarily to the distresses of the sick."[1] These are the opening sentences of William Heberden's *Commentaries on the History and Cure of Diseases*, published in 1802, the year after his death. The thought which they convey will serve as a text for the remarks which follow.

Any person with a disorder of the heart or circulation, regardless of its cause or the degree of functional impairment, too often is looked upon as an invalid. His condition is a cause for concern. Accordingly, it is common practice to classify him as unfit to pursue his customary way of living and advise that he follow regulations which, in varying degree, restrict his activities and curtail his pleasures. To consider the basis for some of these restrictions and to inquire into the reasons why physicians are so ready to impose them is the aim of this discussion.

SMOKING

Patients with any form of heart disease usually are advised to abstain from the use of tobacco. Yet it has been our experience that, over a period of years, most of these individuals can smoke moderately without apparent harm. If one may judge by the amount of tobacco consumed, smoking affords a good deal of pleasure to a large number of persons; for many it provides emotional stability.

Numerous studies have been made of the effects of smoking on the circulation. It is doubtful whether the prolonged use of tobacco is a contributing cause to the production of atheromatosis. The more immediate effects can readily be observed. These are due almost entirely to nicotine. In our laboratory it has been demonstrated that, in the individual, the degree of reaction varies directly with the nicotine content of the smoke. Estimation of cardiac work, using the low frequency, critically damped ballistocardiograph, has indicated that tobacco smoke causes relatively little change in the cardiovascular system. There is considerable variability of effect in both normal persons and patients with heart disease, but this depends to a greater extent on individual susceptibility than on the presence of a cardiac disorder. Smoking rarely induces anginal pain, even in patients subject to spontaneous attacks; "tobacco angina" is uncommon. Because of the enjoyment afforded and the feeling of satisfaction obtained, it is our opinion that the majority of patients with inactive forms of heart disease may be permitted to smoke in moderation. Those who are sensitive to nicotine will fare better by abstinence. There are certain conditions in which smoking should be forbidden because any increase in the work of the heart, however slight, is to be avoided. Among these are congestive heart failure, the acute stages of cardiac infarction and active rheu-

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matic carditis. No patient with peripheral vascular disease should use tobacco because of its constricting action on the peripheral vessels.[2]

Stairs

It is traditional that cardiac patients should be cautioned against the ascent of stairs. If this admonition is heeded, it becomes necessary for these persons either to live on the ground floor or to use an elevator. Such arrangements may be difficult or impossible to make and frequently are a source of considerable inconvenience.

It is readily apparent that mounting an ordinary flight of stairs places an added burden of work on the heart and circulation. The factors which determine the importance of such an effort for the patient with coronary heart disease have been the subject of a recent study in which the work of the heart was determined in normal individuals and in patients with coronary heart disease by the use of the ballistocardiograph.[3] The results were compared after ascending an ordinary flight of stairs, descending these stairs and walking on level ground for an equivalent distance. Cardiac work, stroke volume, pulse pressure and heart rate were noted.

It was concluded that the ascent of stairs does not greatly increase the work of the heart. In the patient with compensated coronary disease the response is not significantly greater than after descent. It is only slightly greater than after walking for an equal distance on the level. Furthermore, the stress is of relatively brief duration. In the presence of congestive failure or if anginal pain occurs during the exertion, stairs should be avoided. Otherwise, the coronary patient may take them leisurely and preferably at a pace which he finds agreeable; for it was observed that deliberate retardation, like hurry, may augment cardiac work.

Air Travel

Many persons with known cardiovascular disease choose to travel by air; a considerable number fly from outlying districts or from foreign countries to a medical center for treatment.[4a] Undoubtedly there are numerous others with unrecognized circulatory conditions who use this means of transportation. During the 20 year period 1930–1949, there have been 91 million revenue passengers flown on all scheduled air routes in the United States. Most of the symptoms of discomfort during flight have been of a minor nature and have been due to airsickness rather than hypoxia. There have been 69 in-flight deaths, of which 49 were attributed to cardiovascular disease. The diagnoses in these cases were: myocardial infarction, 20; acute heart failure, 3; unspecified heart disease, 21; cerebral vascular accident, 5. Cardiovascular disease was also regarded as the cause of death in 14 of 23 persons who died shortly after deplaning. It seems likely that excitement, with the attendant increase in cardiac output, blood pressure and heart rate, was as much responsible for the fatalities as were the effects of altitude.[4b]

Patients with coronary heart disease and anginal pain tolerate moderate oxygen want without demonstrable harm and, as a rule, without suffering discomfort.[4c, d] A survey of the literature supports the view that strain of sufficient degree to damage the circulation in compensated cardiac patients does not occur during routine civilian air transport operations which do not exceed altitudes of 8,000 to 10,000 feet. Cabin altitudes with pressurized equipment rarely exceed 7,000 feet. Fatigue following long flights is due primarily to the effects of oxygen want on the central nervous system rather than on the circulation.

It is clear from these facts and figures that flying for the vast majority of cardiac patients may be undertaken without undue risk. The incidence of fatal cardiovascular accidents is exceedingly small and is probably little, if any, greater than might have been observed in this same group of individuals on the ground. Several of the patients, for example, died during physical exertion or after eating a heavy meal in the plane.

There are, however, certain disorders of the heart in which even a slight additional burden placed on the circulation is undesirable. Excitement incident to the trip, delays due to mechanical factors or discomforts resulting from grounding because of weather conditions must

be taken into consideration as well as the effects of mild hypoxia. The important conditions in which air travel is to be avoided are: (1) congestive failure or evidence of a significantly diminished cardiac reserve; (2) active rheumatic carditis; (3) myocardial infarction which has occurred during the preceding three months; and (4) frequently recurring anginal pain, particularly if experienced at rest.

Work and Exercise

Most cardiac patients are able to work and, in fact, do so.[5a, b] There are obvious exceptions, such as those with active rheumatic carditis, chronic congestive heart failure or intractable anginal pain. The type and amount of work will vary. The executive can carry on at his desk; severe damage in a manual laborer may necessitate a change in occupation. Selective placement has demonstrated that in many industries, individuals with heart disease can be employed successfully and, for special groups studied, the attendance records have been as good as the national average for all industrial workers.[5c] Too frequently men or women in business are advised to curtail their activities to a point at which they can no longer continue to hold the jobs to which they are accustomed and which provide them with a livelihood; sometimes they are urged to retire without adequate reason and often with unhappy results. A radical change in working habits should be recommended only after careful consideration of all the factors involved.

A similar approach is indicated with respect to exercise. For those who are accustomed to exercise and enjoy it, leading a sedentary existence entails a distinct sacrifice. The nature and extent of the pathologic lesions, the estimated hazard involved and the functional capacity of the heart in response to effort serve as guides. In every case, the results of the exercise should be carefully observed and the degree of exertion graduated so that no undue strain is placed on the circulation. Because there is no satisfactory clinical measure of the ability of the heart to perform work, a detailed set of directions cannot be outlined; the patient must be the final judge of his capabilities. Golf, shooting, fishing, riding, swimming and even tennis often may be permitted. Squash, for the majority, is too strenuous. For children and young adults with rheumatic heart disease who are at school or college it usually is advisable not to allow participation in highly competitive sports and games.

Bedpan versus Bedside Commode

For many years the impression has prevailed that the use of the bedpan puts a greater strain on the cardiovascular system than does getting out of bed to sit on a commode at the bedside. There have been dissenting opinions; but these have been based entirely on clinical observation, although occasional deaths on the bedpan have occurred.[6a] Recently it has been demonstrated that, in terms of oxygen consumption, the energy expenditure during the use of the bedpan is significantly higher than during defecation on the commode.[6b]

Most patients dislike the bedpan and many resent using it. The sitting or squatting position, with the feet lower than the abdomen, is the natural posture for defecation. With proper help, to swing the legs over the side of the bed and sit comfortably on a commode is certainly easier and pleasanter than to attempt to balance on a metal container uncertainly supported by a wobbly mattress. For the patient in shock after cardiac infarction or for one so weak that he cannot readily sit upright, the bedpan is necessary; otherwise, taking into account comfort, degree of effort and esthetic satisfaction, the commode is to be preferred.

Diet

During recent years increasing attention has been given to the importance of dietary regulation in the treatment of certain cardiovascular diseases. Of these, the three most important have been atherosclerosis, particularly as it involves the coronary arteries, congestive heart failure and hypertensive vascular disease.

The Low Fat, Low Cholesterol Diet.[7] The presence of cholesterol in varying amounts in the lesions of atherosclerosis leaves no doubt that this substance is concerned in the production of the degenerative process. However, the nature of the role that it plays and the mechanisms responsible for its deposition in the

intima of the arteries are far from clear. There has been a tendency to stress the relatively high level of cholesterol in the serum of patients with coronary heart disease; but it has become apparent that the cholesterol-phospholipid ratio is of greater significance than the level of cholesterol alone. A special class of cholesterol-bearing lipid and lipoprotein molecules likewise have been studied by means of the ultracentrifuge and their presence in excessive numbers has been pointed to as the characteristic feature of the blood in individuals predisposed to atheromatous lesions.

Restriction of cholesterol and fat in the diet has been recommended as a means of arresting the disease and it has even been intimated that the process might be reversed. But the effects on intimal lipid deposits are not known. In order to diminish significantly the cholesterol content of the serum or lower the number of large cholesterol-bearing lipid molecules by dietary restriction it is necessary, in most cases, to cut the intake to extremely low levels. Vegetable as well as animal fats must be rigidly controlled. Since acetate precursor for synthesis is readily available in dietary protein and carbohydrate as well as in fat, restriction of preformed cholesterol can have only a limited effect. The factors which influence the rate of synthesis remain to be determined; it seems possible that elevation of cholesterol may be due to loss of power of the body cells properly to metabolize it, as occurs in normal persons. This would indicate an inherent metabolic defect. Certain it is that in many patients with proved atherosclerotic lesions, the level of cholesterol and the number of larger lipid molecules in the serum may be within the normal range.

The production of atherosclerosis in dogs, rabbits and chickens has afforded a method for study which is yielding valuable information, but because the conditions of the experiments are so far removed from those existing in man, the results thus far cannot be applied directly to human pathology.

The low fat, low cholesterol diet is not interesting. It eliminates from the menu such items as egg yolk, whole milk, cream, butter and vegetable as well as animal fats. These are the staples of good cooking. Until more specific knowledge is available and more convincing evidence has been adduced that such drastic limitation will prevent or retard the development of arterial degeneration it seems unnecessary, and indeed unwise, to institute this type of regimen in patients in whom the disease has made itself manifest. To inflict it upon a large segment of the population because certain changes are found in the blood which it is believed predispose to atheroma is indeed premature prophylaxis. The cause of atherosclerosis in man remains obscure, but the attack on the problem has been initiated. Development of rational therapeutic procedure must wait for further knowledge.

Salt.[8] It is standard practice to prescribe a diet low in sodium in the treatment of congestive heart failure and its value has been demonstrated by years of experience. The mere presence of a cardiac disorder, however, is not an indication for the institution of a low salt diet. This seems obvious, but not infrequently the chore of providing saltless food is placed needlessly on a member of the family and the patient is obliged to partake of meals which lack flavor.

In the presence of congestive failure, sodium restriction may be of varying degree; it is not always necessary that it should be as nearly absolute as possible. In the milder cases food may be served as ordinarily seasoned in the kitchen but no salt is added at table and salty items are omitted. These include ham, bacon, salted fish, salted nuts, potato chips and olives.

Drastic limitation of salt intake in heart failure is not entirely without its dangers, particularly when combined with the continued administration of a mercurial diuretic. There may result serious disturbances in electrolyte metabolism and these, in themselves, may prevent satisfactory diuresis. A patient may become refractory to a mercurial because of the development of hypochloremic alkalosis or of sodium depletion. Correction of electrolyte balance will usually permit of continued administration of the drug with good effect. A routine system for treating heart failure by means of salt restriction, digitalis and a mercurial is to be frowned upon; no routine is ever sound therapeutic procedure. When loss of fluid is ex-

treme or when the usual measures fail to initiate diuresis chemical control is advisable.

Limitation of salt intake has been employed also in the management of patients with hypertensive vascular disease. Its value is still a matter of controversy. There is reason to believe that there exists a disturbance of salt and water metabolism in this condition and controlled studies have suggested that in some patients blood pressure levels may be slightly lowered by extreme restriction. Blocking of the pressor activity of the adrenal cortex has been postulated as a possible mechanism for the depressor effect of low sodium diets.

There is, at present, inadequate information concerning the influence of prolonged and rigid salt deprivation on the natural history of hypertensive vascular disease. Its course is variable and is influenced by many factors as yet imperfectly understood. Many persons with elevated blood pressures, particularly women, live long and actively. It seems unlikely that salt restriction is the most important aspect of management. Additional basic facts concerning etiology must be revealed before it seems fair practice to place the burden of continued marked salt restriction on patients who suffer from a disease of which hypertension is only one manifestation and which may continue for many years. As a practical measure, moderate curtailment, as outlined, may properly be advised. The cation exchange resins have not yet been studied sufficiently to be certain of their effectiveness or harmlessness.

Rice.[9] The monotony of a diet consisting largely of rice is self-evident. In certain patients with advanced hypertensive cardiovascular disease strict adherence to this regimen for several months has been followed by improvement in some of the symptoms and signs; in others a fatal outcome appears to have been hastened because of inanition, uremia or the occurrence of a vascular accident in the heart or brain. The rice diet is sometimes useful in tiding a seriously ill patient over a critical period, as the Karell milk diet is often helpful in the acute stage of congestive failure. Prolonged use of rice, even with limited additions, requires strength of character possessed by relatively few; and it is questionable whether the ultimate good accomplished is worth the sacrifice.

Deviation of the Electrocardiogram from the "Normal"

An absolute value cannot be assigned to any biologic measurement. This principle is applicable to the electrocardiogram. There is no standard pattern; there is a range of normal variation. Too often a slight deviation is considered to be sufficient reason for making a diagnosis of heart disease and, in the absence of symptoms or other signs, a program of restricted activity is outlined. Cardiac invalids are thus created and it is extremely difficult, even with the most cogent arguments, to erase the idea of heart disease after it has been once inscribed on the memory. The electrocardiogram does not measure the functional capacity of the heart; it may show the scars of healed lesions which do not interfere in any way with ordinary or even unusual activity. Marked abnormalities are frequently consistent with a normal way of life, as illustrated in the following account.

Case Report. A business executive was first seen in 1930, at the age of 47 years. He complained of mild substernal pain unrelated to exertion. Since youth he had well-marked kyphoscoliosis which was the result of poliomyelitis. At the time of the initial visit (21 years ago) the heart was found to be moderately enlarged. The blood pressure was 136/76.

Between 1930 and 1946, the patient led an active life as president of a large business organization. In 1946, he suffered an attack of cardiac infarction, from which he made a good recovery. After a suitable interval he was able to resume his business life and is still the board chairman of his corporation. The heart increased somewhat in size; the blood pressure remained within the range of normal. There were never signs or symptoms of cardiac insufficiency.

A large series of electrocardiograms has been made. In 1930 only left axis deviation was present. In 1934, the P-R interval had increased to 0.24 second. Following the attack of cardiac infarction there developed complete auriculoventricular heart block together with the pattern of right bundle branch block, and, at times, numerous ventricular premature beats occurred. The complexes underwent frequent changes with the ventricular rate remaining usually at 36 to the minute. In 1949 auricular fibrillation appeared and has persisted. There has

been no essential change in the form of the ventricular complexes during the past two years (fig. 1).

For a long time this man has been sexually impotent and apparently has derived satisfaction from ballroom dancing. Although spinal curvature is marked, he is extremely graceful and is well known in the night clubs of New York as an accomplished performer. He has been permitted to continue with dancing and with his business, and has been able to carry on both without discomfort. Early in 1951, he took a trip to South America and travelled 10,000 miles by air. On his return, he stated that he never felt better in his life.

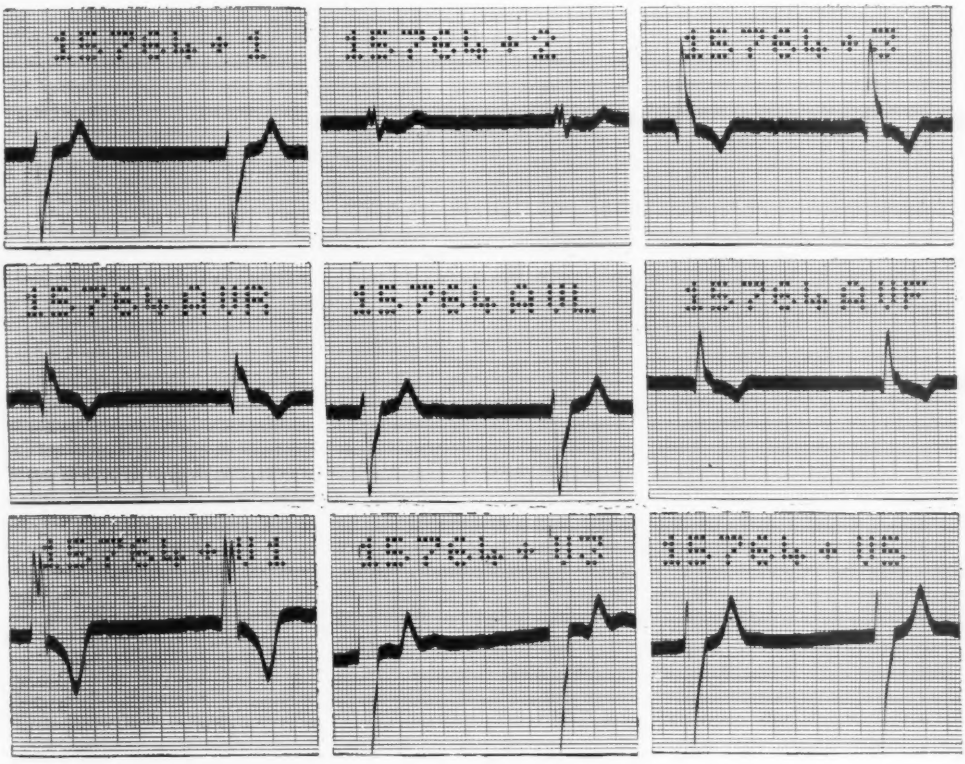

FIG. 1. Electrocardiogram of male, 68 years old, five and one-half years after cardiac infarction. It shows the pattern of complete auriculoventricular heart block, right bundle branch block and auricular fibrillation. The ventricular rate is 36. The patient was not taking digitalis.

The form of the electrocardiogram would lead one to pause before sanctioning such activity. Up to the present, the patient has had five years of full and happy living without evident harm to his condition. His wife and brother have been aware of the possible risk involved and have approved of the course followed.

WHY DOCTORS YIELD

There are numerous reasons for the doctor's readiness to impose restrictions on the cardiac patient. Among them are these: (1) He is dealing with a group of conditions the causes of which, for the most part, are unknown. In his desire to serve his patients, he seizes eagerly on any measure which seems to give promise of amelioration or cure. Too often he is neither sufficiently critical of what appears to be a new advance nor familiar with the reasoning which led to its proposal. (2) He is eager to fulfill the expectations of the patient. The ailing individual usually expects that modifications in his usual regimen will bring about improvement in his condition and is disappointed if he is told

to continue precisely as has been his custom. (3) He aims to protect himself from criticism. If restrictions are imposed on the patient and these are not heeded, no blame can be placed on the doctor should the course be unfavorable or should the patient die. Conversely, if improvement occurs, this is ascribed to having followed the advice given. (4) A great deal of pressure is exerted by the laity. Professional science writers for the daily press and the popular magazines, lacking medical training and on the alert for what they consider to be "news," are prone to report unproved theories and poorly controlled observations as established facts. The lay public, avidly looking for aid in the treatment of conditions for which honest physicians offer no certain hope of cure and too little in the way of effective therapy, is not in a position to exercise critical judgment. If the physician does not subscribe to what are considered the latest innovations, he is labeled ultraconservative or old fashioned. With characteristic insight, George Bernard Shaw appreciated the situation and stated it crisply in the preface to his play, *The Doctor's Dilemma:* "The doctor may lay down the law despotically enough to the patient at points where the patient's mind is simply blank; but when the patient has a prejudice the doctor must either keep it in countenance or lose his patient." Under such circumstances, at the expense of additional time and effort, the physician should assume the role of educator as well as healer.

Summary and Conclusions

A plea has been made for a more generous viewpoint on the part of the physician in planning a therapeutic regimen for the patient with heart disease. Reference has been made particularly to smoking, ascent of stairs, travel by air, work and exercise, use of the bedpan, diets low in fat, cholesterol and sodium, and deviations of the electrocardiogram from the standard pattern. Limitations in all phases of living should be gaged according to the status of the individual and not on a routine basis. It should be the aim of the physician to permit the greatest amount of activity and pleasure which is consistent with the best interest of the patient; for the neurosis induced by unjustified restrictions is often more damaging in its effects than the disorder for which they are prescribed. And a diagnosis of heart disease, once implanted in the mind, is truly difficult to uproot, even though later proved to be false.

Recently it has been estimated that elimination of the cardiovascular-renal diseases would increase the expectation of life at birth almost 10 years for white men and 9 years for white women.[10] Attainment of such an ideal goal is desirable but unlikely. Our span of life is limited both by our own ignorance and by forces which are now, and probably always will be, largely beyond our control. In making regulations for the cardiac patient, as well as for others who are ill, the viewpoint should include a sense of practicability and realism. It is our function as physicians to promote the health of those who come to us for help; in our zeal to prolong life let us not, without good cause, lessen their joy in living.

References

[1] Heberden, W.: Commentaries on The History and Cure of Diseases. London, T. Payne, 1802.

[2a] Levy, R. L., Mathers, J. A. L., Mueller, A. A., and Nickerson, J. L.: Effects of smoking cigarets on the heart in normal persons and in cardiac patients. J. A. M. A. **135:** 417, 1947.

[b] Mathers, J. A. L., Patterson, M. C., and Levy, R. L.: Some effects on the circulation of smoking cigarettes with varying nicotine content. Am. Heart J. **37:** 612, 1949.

[c] Levy, R. L.: Smoking for the cardiac patient, M. Clin. North America **34:** 697, 1950.

[3] Mathers, J. A. L., Griffeath, H. I., Levy, R. L., and Nickerson, J. L.: Effect of ascending an ordinary flight of stairs on the work of the heart: observations on normal individuals and on patients with coronary heart disease. Circulation **3:** 224, 1951.

[4a] Tillisch, J. H., Stotler, J. F., and Lovelace, W. R., II: Study of the effects of airplane transportation of 200 patients. J. Aviation Med. **14:** 162, 1943.

[b] McFarland, R. A.: Human Factors in Air Transport Operations. New York, McGraw Hill Book Co. In press.

[c] Levy, R. L., Barach, A. L., and Bruenn, H. G.: Effects of induced oxygen want in patients with cardiac pain. Am. Heart J. **15:** 187, 1938.

[d] Graybiel, A.: A consideration of the effects of oxygen lack on the cardiovascular system from the point of view of aviation with an analysis of deaths occurring aloft on commercial aircraft. J. Aviation Med. **12:** 183, 1941

[5a] KRESKY, B., AND GOLDWATER, L. J.: Occupational potentialities of cardiac patients. Am. Heart J. **27:** 623, 1944.
[b] GOLDWATER, L. J.: Heart disease and employment. Rhode Island M. J. **30:** 179, 1947.
[c] Staff of Work Classification Unit, N. Y. U. Med. Division, Bellevue Hospital, N. Y.: An occupational analysis of 580 cardiac clinic patients. Circulation **3:** 289, 1951.
[6a] MCGUIRE, J., GREEN, R. S., HAUENSTEIN, V., COURTER, S., BRAUNSTEIN, J. R., PLESSINGER, V., IGLAUER, A., AND NOERTKER, J.: Bed pan deaths. Am. Pract. & Digest Treat. **1:** 23, 1950.
[b] BENTON, J. G., BROWN, H., AND RUSK, H. A.: Energy expended by patients on the bedpan and bedside commode. J. A. M. A. **144:** 1443, 1950.
[7a] BLOCH, K.: The intermediary metabolism of cholesterol. Circulation **1:** 214, 1950.
[b] KEYS, A., MICKELSON, O., MILLER, E. V. O., AND CHAPMAN, C. B.: The relation in man between cholesterol levels in the diet and in the blood. Science **112:** 79, 1950.
[c] GOFMAN, J. W., JONES, H. B., LINDGREN, F. T., LYON, T. P., ELLIOTT, H. A., AND STRISOWER, B.: Blood lipids and human atherosclerosis. Circulation **2:** 161, 1950.
[d] STEINER, A., AND KENDALL, F. E.: Atherosclerosis and arteriosclerosis in dogs following ingestion of cholesterol and thiouracil. Arch. Path. **42:** 433, 1946.
[e] STEINER, A.: Cholesterol in arteriosclerosis, with special reference to coronary arteriosclerosis. M. Clin. North America **34:** 673, 1950.
[f] Cholesterol metabolism and arteriosclerosis. Combined Staff Clinic of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, N. Y. Am. J. Med. **6:** 103, 1949.
[g] GERTLER, M. M., GARN, S. M., AND WHITE, P. D.: Diet, serum cholesterol and coronary artery disease. Circulation **2:** 696, 1950.
[h] MORRISON, L. M.: Arteriosclerosis: recent advances in the dietary and medicinal treatment. J. A. M. A. **145:** 1232, 1951.
[i] HILDRETH, E. A., MELLINKOFF, S. M., BLAIR, G. W., AND HILDRETH, D. M.: The effect of vegetable fat ingestion on human serum cholesterol concentration. Circulation **3:** 641, 1951.
[8a] WHEELER, E. O., BRIDGES, W. C., AND WHITE, P. D.: Diet low in salt (sodium) in congestive heart failure. J. A. M. A. **133:** 16, 1947.
[b] SCHROEDER, H. A.: Renal failure associated with low extracellular sodium chloride: the low salt syndrome. J. A. M. A. **141:** 117, 1950.
[c] STOCK, R. J., MUDGE, G. H., AND NURNBERG, M. J.: Congestive heart failure. Variations in electrolyte metabolism with salt restriction and mercurial diuretics. Circulation **4:** 54, 1951.
[d] AMBARD, L., AND BEAUJARD, E.: Causes de l'hypertension artérielle. Arch. gén. méd. **1:** 520, 1904.
[e] ALLEN, F. M., AND SHERRILL, J. W.: The treatment of arterial hypertension. J. Metab. Res. **2:** 429, 1922.
[f] PINES, K. L., AND PERERA, G. A.: Sodium chloride restriction in hypertensive vascular disease. M. Clin. North America **33:** 713, 1949.
[g] CORCORAN, A. C., TAYLOR, R. D., AND PAGE, I. H.: Controlled observations on the effect of low sodium dietotherapy in essential hypertension. Circulation **3:** 1, 1951.
[h] PERERA, G. A.: The adrenal cortex and hypertension. Bull. New York Acad. Med. **26:** 75, 1950.
[i] DOCK, W., AND FRANK, N. R.: Cation exchangers: their use and hazards as aids in managing edema. Am. Heart J. **40:** 638, 1950.
[9a] KEMPNER, W.: Treatment of kidney disease and hypertensive vascular disease with rice diet. North Carolina M. J. **5:** 125, 273, 1944; Compensation of renal metabolic function. Treatment of kidney disease and hypertensive vascular disease with rice diet. North Carolina M. J. **6:** 61, 117, 1945; Treatment of heart and kidney disease and of hypertensive and arteriosclerotic vascular disease with the rice diet. Ann. Int. Med. **31:** 821, 1949.
[b] WATKIN, D. M., FROEB, H. F., HATCH, F. T., AND GUTMAN, A. B.: Effects of diet in essential hypertension. Results with unmodified Kempner rice diet in fifty hospitalized patients. Am. J. Med. **9:** 441, 1950.
[10] Future Goals in Longevity, Statistical Bull., Metropolitan Life Insurance Co. **32:** 8, 1951.

ABSTRACTS

BACTERIAL ENDOCARDITIS

Correll, H. L., Lubitz, J. M., and Lindert, M. C. F.: Bacterial Endocarditis: Clinico-Pathologic Studies of Untreated, Treated and Cured Patients. Ann. Int. Med. **35:** 45 (July), 1951.

The records of 70 cases of bacterial endocarditis have been analyzed with a view to determining the mortality rate and the factors responsible for the death of patients suffering from this clinical entity. Of the total number, 23 had received only symptomatic treatment, 11 had been treated with sulfonamides and 36 had been treated with penicillin. The only survivors were in the group who had received penicillin therapy. Of the 50 who died, postmortem studies were performed in 22 of the 23 untreated cases, in 8 of the 11 sulfonamide treated cases and in 18 of the penicillin treated cases. Immediate mortality in the untreated, sulfonamide treated and penicillin treated cases was 100 per cent, 100 per cent and 44.4 per cent respectively. However, although 55.6 per cent of the patients receiving effective antibiotic therapy survived the infection, 32 per cent of the survivors had serious impairment of cardiac function, which progressed to death from heart failure within two years in 16 per cent. Altogether, heart failure accounted for death in 100 per cent of the sulfonamide treated cases, in 93.8 per cent of the penicillin treated cases and 39.1 per cent of the untreated cases. The causes of death in the remainder of the untreated cases were cerebral embolism, pulmonary infarction and overwhelming sepsis. Postmortem findings indicated that all deaths from embolic phenomena, uncomplicated by heart failure, occurred in the patients whose vegetations showed minimal healing, thus suggesting that a major effect of treatment in reducing the mortality is to reduce embolism through healing of the vegetation. However, although antibiotic therapy has reduced the hazards of embolism, it has not eliminated heart failure resulting from myocarditis or progressive valvular deformity, particularly of the aortic valve. The occurrence of heart failure during treatment is a most serious prognostic sign. In this series, 87.5 per cent died during treatment or within three months thereafter, and the remaining 12.5 per cent died of heart failure within three years.

WENDKOS

BLOOD COAGULATION

Mangieri, C. N., Engelberg, R., and Randall, L. O.: The Heparin-Like Activity of a New Anticoagulant, Treburon. J. Pharmacol. & Exper. Therap. **102:** 156 (July), 1951.

Studies of the pharmacology of a synthetic anticoagulant, Treburon, are presented. Treburon resembles heparin in many of its properties. In vivo and in vitro it is one-fourth to one-half as active as heparin and is about one-half as toxic. Its anticoagulant action is due primarily to antithrombin activity. It shows scarcely any antiprothrombin activity at low doses and only slight activity at higher doses. It has no effect upon platelet agglutination, sedimentation rate or fibrinogen precipitation. The anticoagulant effect is neutralized by protamine sulfate. At high blood concentrations it is excreted by the kidneys. In subacute toxicity tests there was no adverse effect upon growth or blood formation and spontaneous hemorrhages were not observed.

SAGALL

Laufman, H., Preston, F. W., and Bourdeau, R.: Efficacy of Hemostatic Agents in the Presence of Anticoagulant Therapy. Arch. Surg. **63:** 60 (July), 1951.

The authors attempted to evaluate the therapeutic effect of gelatin sponge as a hemostatic agent in a series of 23 dogs, using the spleen as a test organ. In each instance the coagulation time or the prothrombin level had been previously altered by means of anticoagulant therapy. It was found that when the changes did not exceed the recognized safe therapeutic limits, gelatin sponge effectively controlled bleeding from the spleen. However, when safe anticoagulant levels were greatly exceeded, the use of gelatin sponge could not be depended upon.

ABRAMSON

Collentine, G. E., and Quick, A. J.: The Interrelationship of Vitamin K and Dicoumarin. Am. J. M. Sc. **222:** 7 (July), 1951.

By the use of cholecystnephrostomy, dogs were rendered extremely susceptible to the action of dicoumarin, probably because the absence of bile salts prevented the storage of vitamin K. After three months, a marked rise in prothrombin time followed the administration of small doses of dicoumarin. An immediate return of prothrombin concentration to normal occurred when vitamin K was injected. The synthetic vitamin K preparations, Hykinone, Synkavite, and Menadione were somewhat less effective in that order in correcting the dicoumarin-induced hypoprothrombinemia. Simultaneous administration of vitamin K and dicoumarin demonstrated that each blocks the action of the other on prothrombin levels.

The authors suggest that vitamin K is a prosthetic group which combines with an apoenzyme to form the active enzyme responsible for prothrombin synthesis. Dicoumarin may act as an antivitamin by displacing vitamin K in this system, thus blocking the synthesis of prothrombin.

SHUMAN

Bjerkelund, C. J.: A Comparison between the Effect of Intravenously and Orally Administered Dicoumarol on the Plasma Prothrombin Levels in Man. Scandinav. J. Clin. & Lab. Investigation **3:** 115, 1951.

In any one individual the effects of identical oral and intravenous doses are very similar. Hypoprothrombinemia develops with equal speed in both cases. The authors feel that injections of dicumarol are therefore not indicated as an initial treatment, except in vomiting or diarrhea.

OPPENHEIMER

CONGENITAL ANOMALIES

Warkany, J.: Congenital Anomalies. Pediatrics **7:** 607 (May), 1951.

The author deprived pregnant female rats of certain essential nutritional elements. The depletion in the mother of specific factors resulted in specific congenital defects in the offspring. Vitamin D deficiency caused bowing of the bones of the forearms and legs; riboflavin lack resulted in cleft palates, syndactylism, fusion of the ribs, shortening of the bones of the jaw, forearms, and legs; vitamin A depletion produced anomalies of the heart, diaphragm and urogenital organs. Human dietary conditions were not simulated. The author does believe that dietary deficiency in the United States is a factor in the development of congenital anomalies. However, in populations with a constant restriction in food supply, this may be a factor. It is pointed out that environmental changes such as deficiency states can result in congenital defects which previously had been thought to be hereditary in nature.

MARGOLIES

Levinson, D. C., Cosby, R. S., Griffith, G. C., Meehan, J. P., Zinn, W. J., and Dimitroff, S. P.: A Diagnostic Pulmonary Artery Pressure Contour in Patent Ductus Arteriosus Found during Cardiac Catherization. Am. J. M. Sc. **222:** 46 (July), 1951.

Two patients with patent ductus arteriosus were studied by cardiac catheterization prior to surgical ligation of the ductus. In both instances, a characteristic pulse pressure contour was obtained by continuous recording of the pressure while the catheter was slowly withdrawn from the right pulmonary artery into the right ventricle. The change consisted of an abrupt rise in the systolic and diastolic pressures at the site of the ductus. This rise in pressure is accompanied by an alteration of the pulse contour. It is believed that these local changes represent the transmission of systemic pressure through the patent ductus.

SHUMAN

Abrams, H. L.: Left Ascending Aorta with Right Arch and Right Descending Aorta. Radiology **57:** 48 (July), 1951.

The author describes the roentgenologic findings in this rare aortic anomaly. These are a right aortic arch with its impression on the esophagus from the right; a descending aorta visible on the right side; compression of the trachea by the anteriorly situated transverse portion of the aortic arch.

At autopsy the roentgenologic findings were confirmed. The aorta arose from a single ventricular chamber, to the left of the midline, coursed upwards on the left side, crossed the midline anterior to the trachea, compressing it, then descended on the right side.

SCHWEDEL

Cosby, R. S., Levinson, D. C., Griffith, G. C., Zinn, W. J., and Dimitroff, S. P.: Clinical and Cardiac Catheterization Studies in Four Cases of Eisen-

menger's Complex. Am. J. Med. **11:** 31 (July), 1951.

Data obtained by cardiac catheterization of four patients with Eisenmenger's complex are presented. Right ventricular hypertrophy was shown electrocardiographically and by unusually high systolic and diastolic pressures in the right ventricle and pulmonary artery. The ventricular septal defect was demonstrated in three patients by a rise in the oxygen content of the blood in the right ventricle over that in the right auricle or, in a high ventricular septal defect, by a rise in the oxygen content of the blood in the pulmonary artery over that in the right ventricle. In a single patient the catheter passed directly through the defect into the left ventricle. Evidence for overriding of the aorta was also obtained. In two patients pulmonary pressures exceeding systemic pressures were attributed to increased pulmonary resistance.

HARRIS

Wüthrich, R.: Origin of the Left Coronary Artery from the Pulmonary Artery. Contribution to the Problem of Sudden Death. Cardiologia **18:** 193, 1951.

Among 15,000 autopsies with 123 instances of congenital malformation of the heart the author found two cases with an anomalous origin of the left coronary artery from the pulmonary artery. The first was an infant who died at the age of four months from progressive heart failure. Autopsy revealed marked dilatation of the left ventricle with formation of an apical aneurysm and recent and old, partly calcified foci of necrosis of the myocardium, and endocardial fibrosis. The second case, a 27 year old man, had never shown symptoms or signs of heart disease and died suddenly while swimming. Necropsy showed large areas of recent and healed necrosis and compensatory dilatation of the right coronary artery. Microscopic examination in both cases showed wide blood sinusoids within the myocardium of the left ventricle.

The diagnosis of aberrant origin of the left coronary artery is suggested clinically in an infant by the development of heart failure in the absence of cyanosis and murmurs, and by the typical electrocardiographic pattern of anterior wall infarction. Asymptomatic survival to a higher age is possible, due to anastomotic vessels which develop into wide blood sinusoids within the myocardium and are supplied by a dilated right coronary artery and/or from the ventricular cavities by the thebesian circulation.

PICK

Gotzsche, H., Eskilden, P., and Hansen, A. T.: Isolated Pulmonary Stenosis. Acta med. Scandinav. **139:** 431, 1951.

The authors have observed 31 cases of isolated pulmonary stenosis in a group of 340 patients with congenital heart disease. The diagnosis was based upon the demonstration of pulmonary stenosis by cardiac catheterization and the absence of signs of other cardiac anomalies. In some patients the right ventricular pressure was higher than the systemic arterial blood pressure and in one patient it was 205/0 mm. Hg. Except for one patient, cyanosis was absent. There was no proportionality between the degree of pulmonary stenosis as judged from the right ventricular pressure and the degree of cardiac discomfort. All patients had a harsh, systolic murmur, most intense along the left sternal border, usually in the second intercostal space. The pulmonic second sound was usually louder than the aortic second sound and in only one-third of the cases was the pulmonic second sound faint or inaudible. Right axis deviation was present in the electrocardiograms in one-half of the patients. The type of pulmonary stenosis is suggested by the findings on catheterization: (a) valvular stenosis is said to produce a sudden change in the pressure tracings from the pulmonary shape to the ventricular when the tip of the catheter is withdrawn through the pulmonary ostium; (b) a long infundibular stenosis is associated with a more gradual transition in the pressure curves; and (c) a localized subinfundibular stenosis is accompanied by a normal transition at the pulmonary ostium but a sudden rise when the catheter tip is farther down in the ventricle. Roentgen studies disclosed a prominence of the second left arch and normal or faint vascular markings in the lungs or aplasia of the pulmonary conus. The prominence is attributed to poststenotic dilatation.

ROSENBAUM

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Griepentrog, F.: Chronic Ventricular Aneurysm with Angina Pectoris Due to Hypoplasia of a Coronary Artery. Ztschr. f. Kreislaufforsch. **40:** 432 (July), 1951.

The author reports the unusual case of an aneurysm of the right ventricle due to hypoplasia of the right coronary artery. An autopsy was performed on a 31 year old man who died suddenly. He gave a history of frequent anginal seizures during a period of several years. The left ventricle was macroscopically normal and showed a few scars on histologic examination. The tricuspid ostium and the right ventricle were considerably dilated with marked thinning of the posterior wall of the latter. The circumference of the right coronary artery at its origin measured about half that of the left coronary and remained so in its further course. The thickness of the intima was equal in both vessels and there were no signs of atherosclerosis. Microscopic examination of the myocardium in the region of the aneurysm showed typical chronic fibrosis, but no signs of recent necrosis. The author considers insufficient blood supply to the right ventricle by the hypo-

plastic right coronary artery a primary factor in the pathogenesis of the myocardial lesion.

PICK

Bing, R.: The Coronary Circulation in Health and Disease as Studied by Coronary Sinus Catheterization. Bull. New York Acad. Med. **27:** 407 (July), 1951.

The coronary circulation in man was studied by means of an intracardiac catheter introduced through the right auricle into the coronary sinus. Withdrawal of coronary sinus blood after saturation of the heart muscle with nitrous oxide afforded a means of measuring the coronary blood flow through a unit of left ventricular muscle. The oxygen consumption of the same unit of myocardial tissue could be determined by comparing the coronary sinus and arterial oxygen content. From this the energy cost and efficiency of the work of the left ventricle could be calculated. In normal man the average coronary blood flow is 77 cc. per minute through 100 Gm. of left ventricular tissue with an oxygen consumption of 9.4 cc. per minute and an average oxygen extraction of 12 volumes per cent. The coronary blood flow represents only about 5 to 10 per cent of the cardiac output indicating that the metabolic requirements of the heart are fulfilled by a large oxygen extraction rather than by a large blood flow.

Comparisons were made between the coronary flow, oxygen evacuation and oxygen consumption per unit weight of normals and of patients with thyrotoxicosis, mild and severe anemia, peripheral arteriovenous fistula, essential hypertension, coarctation of the aorta, myocardial infarcts and congestive heart failure. The author's findings indicate that in vivo the failing heart is unable to convert oxidative energy into useful work since the oxygen consumption of the myocardium is normal despite an increase in diastolic fiber length. Digitalis preparations do not correct this fundamental defect and increase cardiac efficiency only by increasing the cardiac work by raising the cardiac output.

SAGALL

Eckerstrom, S.: Clinical and Prognostic Aspects of Acute Coronary Occlusion. Acta med. Scandinav. Suppl. **250:** 1, 1951.

The author reviews the literature dealing with the various clinical aspects of acute myocardial infarction and records his own observations in 242 cases. Transitory hyperglycemia was observed in 111 of 162 nondiabetics in this series, with blood sugar concentration values of 150 mg. per 100 ml. or more in half of them. This symptom had no clear prognostic value and it is the author's belief that no satisfactory explanation could be found for it. In the frank diabetics of this series, the early mortality and the mortality within four years was significantly greater than in the nondiabetics.

Fever occurred in 79.3 per cent of the cases. The opinion is expressed that the degree and duration of fever is of no prognostic value in uncomplicated acute coronary occlusion. The temperature generally rose on the day of onset or on the following day and tended to reach its maximum on the second or third day. In some cases the fever persisted into the second or third week even though no complications were demonstrable. The sedimentation rate rose in all but 15 of the 112 cases who survived the first week without complications. The range of increase was very wide and no correlation could be demonstrated between the sedimentation rate and the prognosis. Leukocytosis occurred in 164 of 206 patients examined; maximum values were most frequently recorded on the second and third day after the onset. There was no correlation between mortality and the frequency or degree of leukocytosis.

The mortality during the first four weeks was 55 per cent and 69.8 per cent within the first year. Obesity and coexistent hypertension did not seem to influence the mortality significantly. The immediate mortality was 69.4 per cent in patients with congestive heart failure complicating acute coronary occlusion and only 53.4 per cent in those without this complication. This same difference in prognosis in patients with congestive failure was manifest in follow-up periods of one year and four years. There was no apparent difference in the mortality rate in those cases with painless myocardial infarction from those with cardiac pain.

Twelve patients were re-examined at intervals of 4 to 11 years after the acute coronary occlusion. No clear signs of diabetes had appeared in those patients of this group who demonstrated transitory hyperglycemia during the acute attack. All but one of them showed some subjective or objective evidence of heart disease.

ROSENBAUM

ELECTROCARDIOGRAPHY

Boden, E., and Gillman, H.: Experimental Investigations in the Isolated Mammalian Heart for Interpretation of Positional Changes of the Electrocardiogram. Arch. f. Kreislaufforsch. **17:** 117 (July), 1951.

The authors studied experimentally the effect of rotation of the heart along various axes on the vectorcardiogram. Vector loops were obtained by construction from three bipolar leads arranged in form of an equilateral triangle around an isolated and perfused heart of a dog, cat or rabbit.

Rotation of the heart along its sagittal axis produced changes in all three leads; rotation along the longitudinal axis changed mainly lead III, and rotation along a transverse axis, mainly leads II and III. Shifting of the heart, without rotation, on the sagittal axis did not alter the electrocardiogram.

In the presence of an abnormal T vector, especially

if the latter is deviated to the left, rotation of the heart on the longitudinal, sagittal axis, as well as on a vertical ("mediastinal") axis, changes the electrocardiogram to a typical hypertrophy curve with discordant R and T waves. With rotation of the heart on the horizontal, vertical or longitudinal axis, the vector loop may assume a sagittal position, and thus abnormal low voltage in the electrocardiogram may result. Monophasic deformation of ST-T, effected by injecting jodipin into a coronary artery, may be accentuated or may disappear with rotation of the heart in various directions.

PICK

Lasser, R. P., and Grishman, A.: Spatial Vectorcardiography in Children: An Analysis of High R Waves in Right-Sided Chest Leads. J. Pediat. **39:** 51 (July), 1951.

There is no apparent simple method by conventional electrocardiography of differentiating the electrocardiograms of right ventricular hypertrophy due to congenital heart disease from those frequently encountered in normal young children. The authors made a vectorcardiographic study of normal infants and children and compared them with vectorcardiograms from children with right ventricular hypertrophy from congenital heart disease. It was clearly demonstrated that the vectorcardiograms of the normal infants and young children were definitely different from those of the children with right ventricular hypertrophy. The horizontal plane vectorcardiogram of the normal children showed a large initial anterior loop which is largely counterclockwise in rotation, inscription of the centripetal limb posterior to the centrifugal, and inscription of the major portion of the loop anteriorly. In the children with congenital heart disease, the vectorcardiograms revealed a small initial loop, clockwise rotation, and inscription of the centripetal limb anterior to the centrifugal one.

MARGOLIES

Burstein, C. L., Zaino, G., and Newman, W.: Electrocardiographic Studies during Endotracheal Intubation. III. Effects during General Anesthesia and Intravenous Diethylaminoethanol. Anesthesiology **12:** 411 (July), 1951.

Electrocardiograms were obtained in 114 anesthetized adult patients who were intubated during anesthesia with various agents and in whom diethylaminoethanol (DEAE), a primary hydrolytic product of procaine, was administered intravenously prior to endotracheal intubation. At the time of intubation 12 per cent of the cases showed electrocardiographic disturbances, which consisted mainly of sinus tachycardia and ventricular extrasystoles. In a previous series without diethylaminoethanol, the incidence was 68 per cent. Topical cocainization of the pharynx and larynx during general anesthesia appeared to increase the cardiac disorders. The incidence and severity of cardiac arrhythmias usually encountered at the time of endotracheal intubation was reduced and alleviated by diethylaminoethanol. Diethylaminoethanol is less toxic than procaine and its effective dose is at least 10 times that of procaine.

SAGALL

Virtue, R. W., and Pierce, A. F.: Electrocardiographic Studies during Induction of Anesthesia Using Ethyl Chloride, Ether, Vinethene and Cyclopropane. Anesthesiology **12:** 442 (July), 1951.

Electrocardiograms obtained in 106 patients in whom ethyl chloride was used for induction of anesthesia to the point of loss of consciousness revealed no arrhythmias which contraindicate the use of ethyl chloride for the induction of ether anesthesia. During third stage anesthesia with ether, vinethene or cyclopropane, a wandering pacemaker was frequently observed. This change occurred when the oxygenation of the hemoglobin was 97 to 98 per cent of saturation.

SAGALL

Storch, S., and Master, A. M.: RS-T Segment, T Wave and Heart Rate after Two Step and 10 Per Cent Anoxemia Tests. J.A.M.A. **146:** 1011 (July 14), 1951.

The Master two-step test and anoxemia test of Levy are accepted as useful objective tests in the diagnosis of coronary artery disease. For this study these tests were carried out on 23 patients who had normal resting electrocardiograms but histories of precordial pain of varying degrees of severity. In this study the two-step test was more sensitive, being positive in six patients who were known to have organic heart disease where the anoxemia test was negative in the same six cases. A positive anoxemia test was considered reliable, but a negative one was not found to be dependable. No side reactions occurred in any of the patients during the two step exercise test. One patient developed a shocklike state, one severe cyanosis, and severe precordial or substernal pain was noted in five others during the anoxemia test. This paper demonstrates that there are many differences in the electrocardiographic responses produced by the two tests and they cannot be used interchangeably.

KITCHELL

Soloff, L. A., and Zatuchni, J.: On the Apparently Absent Q Wave in Left Bundle Branch Block. Am. J. M. Sc. **222:** 18 (July), 1951.

According to the classic Wilsonian interpretation, the Q wave commonly seen in electrocardiographic leads over the left ventricle arises from the activation of the septum by the left bundle. In left bundle branch block, according to this theory, the Q wave in these leads disappears as activation is now accomplished from the right side; however, when septal

infarction is present with left bundle branch block, activation of the right ventricular muscle will produce an initial negative deflection in leads derived from the left ventricle. The authors have studied 13 patients with left bundle branch block using fluoroscopy to determine the relationship of the heart to the thoracic wall, and with multiple thoracic electrocardiographic leads in order to derive the spatial QRS vectors and to determine whether the Q waves represent different projections of the initial portion of the electrical forces. The vector loops of two cases are presented in detail. The vectorcardiographic studies aided the authors in predicting areas of the body surface where Q waves would be manifested in the electrocardiogram. It was concluded that the presence or absence of a narrow Q wave in a given electrocardiographic lead depends upon the location of that lead with reference to the left ventricle. Abnormal Q waves (0.04 second, slurred, notched) in left bundle branch block seen in leads over the left ventricle are indicative of myocardial infarction and represent a manifestation of focal block in the region of the infarcted muscle.

SHUMAN

Graettinger, J. S., Packard, J. M., and Graybiel, A.: A New Method of Equating and Presenting Bipolar and Unipolar Extremity Leads of the Electrocardiogram. Advantages Gained in Visualization of Their Common Relationship to the Electric Field of the Heart. Am. J. Med. **11:** 3 (July), 1951.

The authors suggest increasing the sensitivity of the electrocardiographic recorder in unipolar extremity leads, reversing polarity in certain leads, and mounting the 12 bipolar and vector unipolar extremity leads to conform with a hexaxial reference system. They find these modifications in electrocardiographic technic give the following advantages: (1) the relationship between the bipolar and unipolar limb leads immediately becomes clear; (2) the transitions in form of P, QRS, and T around the entire electric field can readily be observed and measured; (3) estimation of the mean vectors of P, QRS, and T in the frontal plane can be done by inspection, and (4) the changes in direction of the excitation wave during the depolarization process can be estimated.

HARRIS

Shaffer, C. F., and Chapman, D. W.: The Exercise Electrocardiogram. Am. J. Med. **11:** 26 (July), 1951.

The exercise electrocardiogram was of aid in the evaluation of 20 patients with the single electrocardiographic abnormality of a deep Q_3. Ten patients had had myocardial infarctions one to five years prior to examination. Of these, five showed positive exercise tolerance tests. The remainder were negative. The authors believe a positive exercise tolerance electrocardiogram is fairly reliable evidence of coronary artery insufficiency in patients with no other alteration in the routine electrocardiogram than a large Q_3.

HARRIS

Boyadjian, N., and Van Dooren, F.: Shortening of the QRS Complexes in Intraventricular Blocks following Changes of Rhythm. Considerations on the Refractory Period and the Supernormal Phase of Excitability of the Intraventricular Conduction Tissue. Acta cardiol. **6:** 254, 1951.

The authors report eight cases of intraventricular block with variations of the QRS duration. In one group (three cases) they observed shortening of the QRS duration with slowing of the sinus rate or after a long postextrasystolic interval. In the five other cases the intraventricular conduction time was reduced, with beats occurring prematurely. In two cases the atrioventricular and intraventricular conduction time improved simultaneously.

The authors feel that the best explanation of the phenomenon seen in the first group is recovery of the specific intraventricular system following an exceptional prolongation of diastole. In the second group they assume the presence of a supernormal phase of recovery of intraventricular conduction to account for the apparent improvement of conduction with a shortened ventricular interval. They stress the rarity of both observations, which can be considered evidence of functional impairment of intraventricular conduction similar to that demonstrated previously for A-V conduction.

PICK

Sjöstrand, T.: The Electrocardiographic Work and Hypoxemia Tests. Scandinav. J. Clin. & Lab. Investigation **3:** 1, 1951.

The author recommends the stationary bicycle ergometer as a means of measuring increased demands on the circulation. The amount of work is measureable and can be gradually increased until signs of insufficiency appear. Pulse, respiration, and electrocardiograms may be observed during and after the test. Abnormalities which do not appear at rest thus may become apparent during additional stresses. Three unipolar leads, one at the midaxillary line at the level of the apex, a second at the apex, and a third at the left border of the sternum in the fourth intercostal space, are recommended. The indifferent electrode is placed on the forehead. With this test coronary insufficiency can be demonstrated before the onset of pain.

Hypoxemia is produced by 9 to 10 per cent oxygen in nitrogen for 8 to 20 minutes. Pain terminates the test if it appears. This test can not be standardized by controlling the amount of oxygen in inspired air since some respond to low oxygen by hyperpnea while others are not much stimulated. Thus the arterial oxygen unsaturation produced is variable,

due to the different pulmonary ventilation resulting from a standard reduction in oxygen in inspired air. Poor ventilation of the lung, as in emphysema, is also a factor. The ear oximeter can be used to evaluate the amount of depression in arterial oxygen level. These difficulties in standardizing hypoxia tests make the author prefer the graduated work load. Caution is advised in interpreting the electrocardiogram, since it is difficult to differentiate between coronary insufficiency and other conditions where pain is concerned. Some electrocardiographic changes normally result from alterations in hemodynamics (Sjöstrand, 1950) and must be separated from a pathologic reaction. Both T waves and S-T segments are involved. A high T wave which follows work closely is probably due to tachycardia, but if it is apparent three to five minutes later when the pulse is slower it may be considered pathologic. In real insufficiency electrocardiographic changes are much greater after work or hypoxia than after amyl nitrite or scopolamine. Only clearly marked electrocardiographic changes should be considered pathologic. No serious complications have been seen in 5000 work tests or 3000 hypoxia tests.

OPPENHEIMER

Ljunggren, H.: The Clinical Significance of a Deep Q Wave in the Third Lead of the Electrocardiogram. Acta med. Scandinav. **139:** 176, 1951.

A group of 137 patients without myocardial infarction whose initial electrocardiograms disclosed Q waves in lead III meeting the criteria of Pardee, were followed to their death or re-examined after an interval of 7 to 11 years to determine whether this electrocardiographic abnormality is of importance in the detection of heart disease. The author found in this series of cases that the Pardee Q_3 wave had no value as a reliable criterion of clinically important heart disease. It was his impression that so-called unipolar leading from the left leg appears to be valuable for the evaluation of Q_3 due to posterior myocardial infarction.

ROSENBAUM

Dreyfuss, F., and Diengott, D.: The Value of the Measurement of the Q-T Interval in a Series of Clinical Electrocardiograms. Cardiologia **18:** 213, 1951.

The authors determined the Q-T interval, according to the method of Taran and Szilagyi, in 303 electrocardiograms of patients with various diseases. In 144 cases they found the $Q\text{-}T_c$ longer than the 0.42 second accepted as the upper limit of normal. In 58 instances this was the only electrocardiographic abnormality. The highest values of $Q\text{-}T_c$ were present in cases with high blood pressure. Less marked prolongation (0.42 to 0.43 second) was found in rheumatic and arteriosclerotic heart disease. A prolongation was further found in several cases with liver and kidney disease, in D-hypovitaminosis, in various infections, and in cases with metabolic disturbance and coronary insufficiency. The authors conclude that the Q-T interval is a sensitive indicator of cardiac impairment in a number of pathologic states and its determination should, therefore, be included in clinical electrocardiography.

PICK

Doumer, E., Lorriaux, A., and Dumez, L.: Paroxysmal Tachycardia and the Syndrome of Wolff-Parkinson-White. The Relation of Manifestations of Auricular and Ventricular Activity by Mechanical Action. Acta cardiol. **5:** 243, 1951.

Electrocardiograms are presented of two cases of supraventricular paroxysmal tachycardia with superposition of P waves upon T waves. In one case the end of the attack and in the other both onset and end of the attack were recorded. On the basis of their analysis of the tracings the authors reject the possibility of an auricular tachycardia. They believe that the tachycardia originated in the A-V node, and that the auricles were activated not by retrograde conduction, but by mechanical stimulation effected by the ventricular contraction. One of the cases showed in later tracings a typical Wolff-Parkinson-White syndrome. The authors feel that the concept of a hyperexcitable ventricular focus as the explanation of the Wolff-Parkinson-White syndrome is supported by the association of this syndrome with the described type of paroxysmal tachycardia.

PICK

ENDOCRINE EFFECTS ON CIRCULATION

Bortin, M. M., Silver, S., and Yohalem, S. B.: Diagnosis of Masked Hyperthyroidism in Cardiac Patients with Auricular Fibrillation. Am. J. Med. **11:** 40 (July), 1951.

In a group of 55 patients showing auricular fibrillation without overt hyperthyroidism, radioiodine excretion and plasma protein-bound studies uncovered eight with masked hyperthyroidism. Six of seven patients treated with radioiodine in dosage calculated to induce remission of their hyperthyroidism reverted to normal sinus rhythm. The seventh patient with long-standing rheumatic heart disease continued to fibrillate.

HARRIS

HYPERTENSION

Beyer, K. H., Ross, C. A., Wiebelhaus, V. D., Waller, W. S., and Schuchardt, G. S.: Vasopressor Components of Pheochromocytomas. Ann. Int. Med. **35:** 117 (July), 1951.

The chemical content of three pheochromocytomas, removed surgically from patients in whom the tumor had been suspected before operation,

have been analyzed. All three contained substantial amounts of pressor agents. In two instances 50 and 90 per cent of the pressor content was identified as *l*-norepinephrine. All the pressor content of the tumors could be accounted for by the presence of *l*-epinephrine and its precursors. These amines were found to be freely ultrafilterable from tumor homogenates, indicating that they were neither bound on nor a part of more complex structures. No conjugated pressor amine could be found in the tumors and no free compound was detected in the urine. In one instance a conjugated compound having the nature of epinephrine was found to be present in urine obtained during a paroxysm of hypertension. The data presented herein are consistent with the hypothesis that Arterenol (norepinephrine) is the immediate precursor of epinephrine in the body, and that within the pheochromocytoma itself there is an impairment of transmethylation of norepinephrine to epinephrine.

WENDKOS

Wolferth, C. C., Jeffers, W. A., Lukens, F. D. W., Zintel, H. A., and Hafkenschel, J. H.: Observations on the Results of Subtotal Adrenalectomy in the Treatment of Severe, Otherwise Intractable Hypertension and Their Bearing on the Mechanism by Which Hypertension is Maintained. Ann. Int. Med. **35:** 8 (July), 1951.

This report is based upon observations made in 23 cases, divided as follows: (1) 11 cases subjected to subtotal adrenalectomy, of which eight have survived for periods varying from five months to more than a year, and (2) 12 recent cases, of which 11 have thus far survived for periods of one to three months. In 15 cases, the operation was limited to adrenalectomy and in eight it was combined with either limited or extensive sympathectomy. These patients had all been refractory to medical treatment and with one possible exception the various combinations of duration of hypertension, blood pressure levels, eye ground changes, cerebral vascular resistance, cardiac deterioration and diminution of renal function caused them to be graded as beyond the stage where good results were to be expected from any of the conventional types of sympathetic nervous system operations that have been employed in the treatment of hypertension. The results are encouraging. Subtotal adrenalectomy alone has reduced the arterial blood pressure in some cases from extremely high levels to a normal range, with marked symptomatic improvement, relief from heart failure, improvement in renal plasma flow and reduction in cerebral vascular resistance. In order to achieve such results, it has been necessary to remove more than 90 per cent of adrenal tissue and create a grade of adrenal cortical insufficiency requiring at least minimal replacement therapy. The combination of subtotal adrenalectomy and sympathectomy has yielded more promising results than adrenalectomy alone, although many more cases and longer periods of observation will be required to warrant a conclusion. In one patient in whom bilateral thoracolumbar sympathectomy and unilateral adrenalectomy had failed to control severe hypertension, the blood pressure has been maintained in a low normal range for over a year following the removal of approximately 90 per cent of the remaining adrenal gland. In five of six cases in which the removal of at least 95 per cent of adrenal tissue was combined with bilateral splanchnicectomy and bilateral sympathectomy, T-12 to L-2 inclusive, the early postoperative fall in pressure has tended to be more satisfactory than that obtained from adrenalectomy alone.

WENDKOS

McCubbin, J. W., and Page, I. H.: Role of Cardioacceleration in Chronic Experimental Hypertention. Am. J. Physiol. **166:** 12 (July), 1951.

Cardiac sympathectomy abolishes cardioacceleration, but chronic experimental hypertension due to buffer nerve section largely persists after this operation. Cardioacceleration plays a definite but minor part in the maintenance of hypertension in dogs with chronic experimental hypertension due to buffer nerve section.

OPPENHEIMER

Schnaper, H. W., Johnson, R. L., Tuohy, E. B., and Freis, E. D.: The Effect of Hexamethonium as Compared to Procaine or Metycaine Lumbar Block on the Blood Flow to the Foot of Normal Subjects. J. Clin. Investigation **30:** 786 (July), 1951.

The authors measured quantitatively the increase of blood flow in the foot of 10 normal males after hexamethonium (C6), using the plethysmographic method, and compared the increase with the presumably maximum flow obtained from regional sympathetic block of the lower extremities. Half the subjects showed a greater increase in blood flow to the foot after 50 to 100 mg. of C6 ion intravenously while the other half had a greater flow after regional extradural or intrathecal block. Changes in skin temperature and digital pulse volume did not accurately reflect changes in blood flow. Although in most instances the average foot and toe blood flow was slightly higher after regional block than after C6, in some instances the values were higher after hexamethonium than after block. The authors suggest that C6, in doses of 50 to 100 mg., produces marked to complete blockade of the sympathetic vasoconstrictor outflow to the foot.

WAIFE

Lowy, S.: A Few Notes on Hypertension. Am. J. of Psychotherapy. **5:** 362 (July), 1951.

A blood pressure rise is an effort response beginning immediately after a muscular effort is intended.

Benign hypertension may be regarded as a pathologically fixed effort reaction. The return of blood pressure to normal after psychotherapy is caused by a reassurance of the brain-mind that there is no need for excessive effort.

Patients with benign hypertension tend to feel rebellious toward authority, and also to feel inadequate. Many choose an occupation below their actual level of capacity, and then further resent their low position. Their constant "intended efforts" to cope with mere living, and their anger toward authority, the world and themselves, cause their hypertension. The advice to avoid excitement and exertions seems to the neurotic patient to deny him the right to act aggressively and to try to better his position in life and forestall his failures, and thus upsets him further.

Renal arteriolar damage in such cases probably reinforces hypertension by sending a "false alarm signal" from the damaged area which seems to call for an effort response. Psychotherapy can reduce neurotic effort drives, thus slowing down further renal damage.

The author believes that frustrated intentions affecting the personality and compensatory intention-complexes are the stressors in benign hypertension.

BELLET

Smirk, F. H.: Methonium Halides in High Blood Pressure. Science **114:** 4 (July 6), 1951.

The author briefly describes the continuous slow subcutaneous injection of penta- or hexamethonium halides. By using an electrically driven syringe with continuous injection over 10 or more days the blood pressure of severe hypertensives has been maintained at approximately normal levels day and night. Rapid clinical improvement was noted. According to the author improvement in papilledema, retinal hemorrhages, encephalopathic attacks, congestive failure, etc., are greatly improved.

WAIFE

Mathisen, H. S.: Arterial Hypertension in Unilateral Renal Disease with Inhibition of Growth, Treated with Nephrectomy. Acta med. Scandinav. **139:** 421, 1951.

A girl, aged 13 years and 10 months, was admitted complaining of headache and vomiting. Her blood pressure was 230/130 mm. Hg, her development was that of a girl aged 10 years, and she had not grown or developed at all for two years. After nephrectomy with removal of a pyelonephritic contracted kidney the blood pressure fell and remained at 100–115/70–85 mm. Hg. Her symptoms cleared and in the course of two years she gained 13.3 Kg. and her height increased by 15 cm. The patient is felt to have exhibited some similarity to so-called renal infantilism.

ROSENBAUM

PATHOLOGIC PHYSIOLOGY

Bernthal, T., and Woodcock, C. C., Jr.: Responses of the Vasomotor Center to Hypoxia after Denervation of Carotid and Aortic Bodies. Am. J. Physiol. **166:** 45 (July), 1951.

The direct responses of the vasomotor center to hypoxia have not been determined beyond question. A fall in blood pressure may be explained on other bases than depression of the vasomotor center. To obtain a more specific indicator of neurogenic vascular reactions the authors used changes of blood flow in a limb separately perfused under controlled hydraulic conditions and connected to the body only by its nerves. The results of these experiments demonstrate clearly that hypoxia may excite increased vasoconstrictor activity in animals deprived of carotid-aortic chemoreceptors. The fall in blood pressure so often seen in hypoxia in such animals usually occurs independently of the changes in activity of the vasomotor centers. Under the conditions of these experiments reactions of the center were less than usual but both excitation and inhibition were seen. The authors suggest that oxygen lack may have direct, simultaneous excitatory and depressant actions on the vasomotor center. Results obtained reflect the algebraic sum of these two opposing influences. These two opposing effects develop at different rates and with different intensities for varying degrees of hypoxia. Important factors independent of the vasomotor center act to lower arterial blood pressure during oxygen lack. Without the chemoreceptors hypoxic excitation of the vasomotor center cannot support arterial blood pressure.

OPPENHEIMER

Atwell, R. J., Hickam, J. B., Pryor, W. W., and Page, E. B. Reduction of Blood Flow through the Hypoxic Lung. Am. J. Physiol. **166:** 34 (July), 1951.

Individual lung blood flows in the dog were measured by the Fick principle while the lungs were breathing separately through a bronchospirometric catheter. When one lung was brought into gaseous equilibrium with the pulmonary arterial blood by rebreathing while the other continued to breathe air, half the animals showed a well marked shift of pulmonary blood flow towards the air breathing lung and away from the rebreathing lung.

OPPENHEIMER

PATHOLOGY

Mowry, R. W., and Bangle, R., Jr.: Histochemically Demonstrable Glycogen in the Human Heart with Special Reference to Glycogen Storage Disease and Diabetes Mellitus. Am. J. Path. **27:** 611 (July), 1951.

The authors, utilizing the new glycogen staining technics of McManus and Lillie, examined blocks of myocardium from 33 unknown infants, from 17

known diabetic patients and 63 non-diabetic patients. Successive blocks were removed in some cases from the heart at increasing time intervals post mortem in order to evaluate postmortem glycogen preservation. The presence of considerable amounts of glycogen was noted in a large number of infantile hearts. Nineteen of 33 such hearts showed the definite presence of glycogen, and in six the amounts were considered as high or greater than noted in glycogen storage disease. Three of the six hearts were enlarged. The glycogen content did not appear to be related to sex. The glycogen was preserved for many hours in such hearts without destruction.

Examination of the hearts of adults showed, contrary to the experiments of others, that non-diabetic hearts contain little glycogen. Ten of 63 hearts showed small amounts. Five of these cases had recent infarction. In contrast, in 17 diabetic hearts, eight contained moderate to marked amounts of glycogen. Of these six were receiving insulin and three cases were well controlled at the time of death. There was wide variation in cardiac glycogen in this group. The differences were not clearly related to severity or the manner or treatment of diabetes.

Within limits the postmortem interval from the time of death to the time of fixation of tissue did not appear to be an important factor in the amounts of remaining glycogen.

In glycogen storage disease the glycogen generally is maintained despite poor fixation of the tissue. The amounts have generally been excessive. With the new methods the authors show that small hearts from infants often contain large amounts of glycogen. The presence of this substance, however, bears no relationship to the size of the heart and the pathogenesis of heart enlargement in glycogen storage disease becomes increasingly complex. The only certain thing so far is that the glycogen in that disease process resists autolysis. However, large amounts of glycogen in small infantile hearts also persisted for many hours, much more resistant to autolysis than the glycogen of adult hearts. The authors suggest that the lower diastase blood level of infants may be a factor.

The previous results of Warren's investigations are verified. While nonspecific, the presence of large amounts of glycogen is confirmatory evidence of diabetes mellitus. The level of insulin dosage bears no relationship. There is no evidence that the presence or absence of glycogen alters the cardiac function.

GOULEY

PHARMACOLOGY

Cheymol, J., Cotteggiani, E., and Gay, Y.: Augmentation of the Effects of Adrenaline and Acetylcholine on the Arterial Pressure following injection of Certain Substances with Curare Effect. Compt. rend. Soc. de biol. **145:** 496 (April), 1951.

Synthetic products of the tetrammonium group exert a curare-like action upon the autonomic nervous system. The authors were able to demonstrate the effect of two such substances, 336 HC and BP 5, upon experimentally produced hypertension and hypotension. Adrenaline hypertension in anesthetized dogs showed further increase, persisting for about an hour, following injection of 500 mg. of 336 HC, and the hypotensive effect of acetylcholine was more marked with simultaneous application of 64 mg. of BP 5. These experimental data should be considered in patients who are submitted to treatment with drugs related to tetrammonium, in order to prevent untowards effects of adrenaline or acetylcholine in usual therapeutic dosage.

PICK

Hilton, J. G.: Rate of Enzymatic Breakdown of Digitoxin. Proc. Soc. Exper. Biol. & Med. **77:** 335 (June), 1951.

The breakdown of digitoxin to digitoxigenin and digitose has been accomplished by hydrochloric acid and by heart and liver extracts. The breakdown by the heart and liver extracts is similar in type and rapidity to that accomplished by hydrochloric acid. The extracts of kidney and yeast were unable to cause the breakdown of digitoxin. The activity of heart and liver extracts appears to be due to some substance present in the tissues and is not due to a pH effect. The presence of this substance in heart and liver tissues which splits digitoxin, and thus changes the solubility characteristics, may in some manner explain the action of digitoxin and its mode of excretion.

Purification of the heart extract yielded a reddish brown solid which had a high enzymatic activity and gave typical protein reactions.

MINTZ

Fawaz, G,. and Fawaz, E. N.: Mechanism of Action of Mercurial Diuretics. Proc. Soc. Exper. Biol. & Med. **77:** 239 (June), 1951.

Mersalyl given intravenously in therapeutic doses had no influence on the respiration of kidney cortical slices of the albino rat at the height of diuresis. Mersalyl had no effect on the succinic oxidase activity of the kidney.

The fact that diuresis caused by mercurials can be inhibited by dimercaptopropanol (BAL) is no proof that mercurial diuretics act by inhibiting the succinic dehydrogenase system of the kidney (SH-containing enzymes). It only means that BAL binds the mercury more firmly than do the tissues. The mercurials can react with proteins other than through SH-groupings, and even if certain SH-containing enzymes are inhibited by therapeutic doses of mercury it does not necessarily follow that SH-containing enzymes are involved in the reabsorption of salt and water from the renal tubules.

MINTZ

Young, W. G., Jr., Sealy, W. C., Harris, J., and Botwin, A.: The Effects of Hypercapnia and Hypoxia on the Response of the Heart to Vagal Stimulation. Surg., Gynec. & Obst. **93:** 51 (July), 1951.

The combined effects on the heart of vagal stimulation and of either hypercapnia or hypoxia were studied on a series of anesthetized dogs. Hypercapnia was produced by using a breathing mixture of 20 per cent carbon dioxide and 80 per cent oxygen. The drop in arterial pH which followed such a procedure was in each instance accompanied by an increase in the duration of cardiac asystole during vagal stimulation. Hypoxia, produced by breathing 10 per cent oxygen mixtures, even when combined with hypercapnia and low blood pH, diminished the effect of vagal stimulation on the heart.

ABRAMSON

Best, M. M., and Coe, W. S.: Effects of Dioxyline Phosphate and Enteric-coated Khellin on Coronary Artery Insufficiency. Am. J. M. Sc. **222:** 35 (July), 1951.

In studying the responses obtained upon drug administration, the authors utilized a series of tests designed to influence the electrocardiograms in 11 patients with coronary artery disease. These included the exercise tolerance of Masters, the anoxemia test of Levy, and the Ergonovine test. Clinical evaluation of the drugs was made by noting the effect upon anginal pain during testing, and upon the number of interval anginal attacks and nitroglycerin consumption. The results showed a return of the induced electrocardiographic abnormalities to normal in approximately 40 per cent of the tests conducted with each drug. Subjective improvement occurred in the majority of patients while taking the drugs, as compared to placebo and control periods. Toxic symptoms of anorexia, nausea and diarrhea occurred in eight patients given enteric-coated Khellin and in three who received dioxyline phosphate.

SHUMAN

Wheeler, C. E., and Curtis, A. C.: Treatment of Cardiovascular Syphilis with Penicillin. Am. J. Syph. **35:** 319 (July), 1951.

The authors report on 21 patients, 13 previously untreated, and eight whose initial treatment, given at least 14 years before, had been grossly inadequate. Of the 21 patients with cardiovascular syphilis, 14 also had neurosyphilis. Four patients had saccular aortic aneurysms; 12 had aortic insufficiency; five had both aortic insufficiency and aneurysm. Sixteen patients had symptoms ranging from pain and dyspnea to congestive failure. Treatment with various dosage schedules of penicillin showed no convincing evidence of adverse effect in the form of the Herxheimer reaction or the therapeutic paradox. There appeared to be no need for preliminary administration of iodides or bismuth. The present follow-up period has been too short in this small number of patients to permit conclusions as to the long term effects of treatment.

WAIFE

Sinclaire, H. A., and Webster, B.: The Problem of the Jarisch-Herxheimer Reaction in the Penicillin Therapy of Cardiovascular Syphilis. Am. J. Syph. **35:** 312 (July), 1951.

The authors review the literature in reference to the Jerisch-Herxheimer reaction following penicillin therapy of cardiovascular syphilis. Data are presented on 53 additional cases of cardiovascular syphilis treated with penicillin. The only symptoms observed were mild temperature rises during the first 48 hours of penicillin treatment in six patients who also had neurosyphilis. Five of these had received heavy metals before penicillin therapy. The authors feel that the dangers of the Jarisch-Herxheimer reaction do not appear significant, and that penicillin is the therapeutic choice in this specific treatment of cardiovascular syphilis.

WAIFE

Askey, J. M.: Digitalis in Acute Myocardial Infarction. J.A.M.A. **146:** 1008 (July 14), 1951.

The authors studied 100 cases of myocardial infarction proved by typical electrocardiographic pattern. Alternate patients were given digitalis in therapeutic amounts and were carried on this throughout their hospital stay. No patient was used in the study who had been on digitalis or quinidine prior to infarction and those with any history of arrhythmia prior to infarction were also excluded. To make the study more definitive patients with serious complications were also excluded. The administration of digitalis in therapeutic amounts started in the first week and continued throughout the hospital stay induced no more ventricular ectopic rhythms or instances of sudden death than occurred in a control group of 50 treated without digitalis. The author feels that the fear of catastrophic arrhythmias should not be cited as a deterrent to the use of average doses of digitalis given for the early signs and symptoms of congestive heart failure in myocardial infarction.

KITCHELL

THROMBOEMBOLIC PHENOMENA

Veal, J. R., and Dugan, T. J.: Peripheral Arterial Embolism, Ann. Surg. **133:** 603 (May), 1951.

The authors present the results of either conservative treatment or embolectomy in 28 cases of peripheral arterial embolism. In all instances paravertebral sympathetic blocks were performed immediately after the diagnosis was made. In 12 of these, following the procedure, the pain was relieved,

the function of the limb was restored, and the skin became pink and warm. In nine of these cases the embolus had lodged in the brachial artery below the profunda branch. Although the immediate results in this group were satisfactory, in the two instances of popliteal embolism there was residual impairment of circulation of the limb. In the last case, one of axillary embolus, the patient developed severe causalgia with hyperhidrosis of the hand and arm.

In the remaining 16 cases, sympathetic nerve block had produced no beneficial results and hence embolectomy was carried out. All the patients were operated upon well under the eight hour period. In 13 cases the operation was successful. Of the three failures, one was the case of an aortic saddle embolus, another a popliteal embolus, and the third, a subclavian embolus. In the last two instances, a severe degree of arteriosclerosis was present; this permitted a fresh thrombus to form at the operative site and also caused interference with proper closure of the incision.

It was concluded that the chances of restoring adequate circulation to a limb following a peripheral arterial embolism are excellent when proper therapy is instituted in the first few hours.

ABRAMSON

Kay, J. H.: The Present Status of Tocopherol and Calcium for Prophylaxis of Post-operative Phlebothrombosis. Yale J. Biol. & Med. **23:** 515 (June), 1951.

The author describes his technic for an antithrombin test, which he prefers to consider as a prethrombotic index. Normally, fibrin formation ceases at dilutions between 1:32 and 1:128. In 246 control cases it was found that a level of 1:8 was associated with a high incidence of thrombosis in patients whose prothrombin time (using lung thromboplastin) was normal or nearly so. Often the low levels preceded the occurrence of thrombosis by only a few hours, hence the test should be done daily.

On the basis of previous work which indicated that effective thrombin inhibitors are those with a tocopherol structure, a group of 457 patients was treated with alpha tocopherol phosphate and calcium gluconate. Only 15 developed 1:8 levels; five of these with clinical evidence of phlebothrombosis. The author concludes that the administration of alpha tocopherol and calcium may reduce the incidence of postoperative thromboembolic complications.

ENSELBERG

Newton, M.: Relationship of Weather to Post-operative Phlebothrombosis. Am. J. Surg. **81:** 607 (June), 1951.

In an attempt to study the relationship of weather to postoperative thrombosis, 66 patients with thrombosis of the deep veins of the leg were matched with 66 normals. It was noted that phlebothrombosis occurred more frequently in the spring and fall than in the summer and winter. The weather at the time of the operation appeared to be of little importance as far as the later development of phlebothrombosis was concerned. A rise in barometric pressure, a fall in temperature, and a fall in relative humidity occurred more frequently in relation to the day that the thrombosis developed than to the same postoperative day in the control series.

ABRAMSON

VASCULAR DISEASE

Bartholomew, R. A., Colvin, E. D., Grimes, W. H., and Fish, J. S.: Incidence and Effects of Vascular Disease in 1,000 Consecutive Pregnancies in Private Practice. Am. J. Obst. and Gynec. **61:** 431 (Feb.), 1951.

By means of routine retinal examinations performed during pregnancy in a group of 1,000 consecutive pregnancies, the authors were able to recognize vascular disease and differentiate it from primary true toxemia. It was their belief that if such tests were performed early in pregnancy, one could predict the development of hypertension in 90 per cent of normotensive cases. Among the criteria utilized was the arteriovenous ratio of the retinal vessels. Mild vascular disease was characterized by AV ratios of 2:3 to 1:2; moderate, by ratios of 1:2 to 1:3; and severe, by ratios of 1:3 to 1:4. The more marked the vascular disease, the earlier was the development of hypertension in pregnancy.

ABRAMSON

Riveros, M., and Pack, G. T.: Glomus Tumor: Report of Twenty Cases. Ann. Surg. **133:** 401 (March), 1951.

The glomus tumor is a deep red to purple or blue structure, sharply demarcated from the surrounding tissues, and bears a histologic resemblance to the normal glomus unit. The tumor is fundamentally of benign character. In the case of the 20 patients with this condition reported by the authors, the location of the tumor was generally in the forearm and fingers, although some of the lesions were also found on the thoracic wall, the scapular region and the knee.

The exquisite pain associated with the glomus tumor is the most pathognomonic symptom. It may be intermittent in character or it may develop only when the tumor is touched. Occasionally, the slightest pressure from clothing or bed clothes will precipitate a paroxysmal attack of agonizing pain. The fear of such discomfort may influence the patient in adopting certain protective habits as preventive measures. In fact, atrophy of the entire arm and

shoulder, presumably due to disuse, has been found to occur in an extremity containing a glomus tumor.

The treatment of the lesion is by means of surgical incision. Sympathectomy or irradiation is of no value.

ABRAMSON

Veal, J. R., Dugan, T. J., Jamison, W. L., and Bauersfeld, R. S.: Acute Massive Venous Occlusion of the Lower Extremities. Surgery **29:** 355 (March), 1951.

The authors report eleven cases of acute massive venous occlusion of a lower extremity which were characterized by extreme pain, prominent venous engorgement and deeply cyanotic skin extending onto the thigh. In some instances the loss of fluid into the tissues of the extremity was so great that systemic shock developed. However, blood transfusions quickly restored the blood pressure. Petechial hemorrhages were often seen. Gangrene occurred in two patients, and in each, amputation was required. In five of the cases the condition followed ligation of a major vein in the treatment of venous thrombosis, while in another it was due to the injection of a sclerosing solution into the veins of the leg.

In the treatment of the condition, sympathetic nerve blocks failed to give relief of symptoms. However, in nine patients, elevation of the limb to a 60 to 75 degree angle and then rapid extension and flexion of the foot, followed by flexion and extension of the thighs, relieved the venous engorgement and produced a good therapeutic effect. The exercise was continued with short intervals of rest until it was noticed that the limb could remain at a high level on pillows without showing a return of venous congestion.

ABRAMSON

Kirschner, P. A.: Limitations of Lumbar Sympathectomy in Far-Advanced Peripheral Sclerosis. Ann. Surg. **133:** 293 (March), 1951.

On the basis of a study of 50 patients with far-advanced peripheral sclerosis, in whom lumbar sympathectomy was performed, the author arrived at certain conclusions with regard to the reasons for failure of this procedure.

It was noted that once tissue death supervened, the outlook for a good or even fair result following sympathectomy was slim, with the result that under such circumstances subsequent major amputation was required. The diabetics with arteriosclerosis obliterans had twice as high a proportion of poor results as the patients with arteriosclerosis obliterans alone.

It was the belief of the author that sympathectomy does not significantly contribute to lowered level of amputation and that the prophylactic value of this procedure in asymptomatic extremities remains to be demonstrated.

ABRAMSON

Blakemore, A. H.: Progressive Constrictive Occlusion of the Abdominal Aorta with Wiring and Electrothermic Coagulation. Ann. Surg. **133:** 447 (April), 1951.

The author reviews the electrothermic method of wiring and coagulating large aneurysms of the main arteries of either syphilitic or arteriosclerotic origin. A 10 meter segment of wire is introduced into the aneurysmal sac and heated to an average temperature of 80 C. for a 10 second period. By this means the distribution and extent of blood clotting is controlled on the basis of differential rate of blood flow, since only the wire within the interior of the aneurysm becomes sufficiently hot to cause a deposit of a clot-stimulating protein coagulum. The portion of wire which crosses the fast-moving blood current of the aorta is cooled so rapidly that it remains uncoated and therefore fails to stimulate clotting where it is not wanted. The electrothermic method of wiring aneurysms is a safe procedure of controlled clotting for progressive endoarterial occlusion of aneurysms of the aorta arising distal to the renal arteries.

Of value as an adjunct to electrothermic coagulation is a method of constrictive, partial occlusion of the abdominal aorta, proximal to the aneurysm through the use of Polythene-dicetyl phosphate film. This procedure helps achieve a satisfactory cure for the condition.

ABRAMSON

Wilson, G., Rupp, C., Jr., Riggs, H. E., and Wilson W. W.: Factors Influencing the Development of Cerebral Vascular Accidents. J. A. M. A. **145:** 1227 (April 21), 1951.

Inability to demonstrate blood vessel pathology at autopsy in many patients dying of cerebral vascular accidents suggests that the basic pathophysiologic defects may be due to local dynamic changes in the blood vessels, such as vasospasm and/or circulatory insufficiency associated with cardiovascular disorders. The authors studied 542 patients; some manifestation of cardiocirculatory insufficiency was evident in history, clinical examination or necropsy in 83 per cent (451 cases). These findings suggest that extracerebral systemic circulatory inadequacy plays an important part in the causation of cerebral vascular accidents. Preventive and therapeutic measures should be directed towards maintaining the general circulatory status at a maximum level.

KITCHELL

Morrison, L. M.: Arteriosclerosis. J. A. M. A. **145:** 1232 (April 21), 1951.

The author believes that atherosclerosis is often a

preventable and in some cases a therapeutically susceptible disease. He believes it is a metabolic disorder based on three complex factors: first is the high fat, high cholesterol diet consumed in areas where atherosclerosis is common; second is a constant disorder in blood lipids and lipoproteins probably due to malfunction of the liver; third is endocrine imbalance affecting certainly the thyroid and the estrogenic and androgenic hormones. He discusses tests for atherosclerosis and favors (1) the blood serum phospholipid: cholesterol ratio, (2) cholesterol partitioning procedures, (3) the optical ultracentrifuge technic. Morrison presents a plan for treatment based on low fat, low cholesterol intake (diet list and sample menu are given); the daily use of lipotropic agents as an aid to the liver in regulating blood lipids, lipoproteins, and blood colloidal systems; and the employment of thyroid extract, estrogen and androgen hormones.

KITCHELL

Dow, J. D.: Venographic Localisation of Incompetent Communicating Veins in the Leg. Brit. J. Radiology **24:** 182 (April), 1951.

Incompetency of communicating veins in the lower extremities is a very important factor in the production of varicosities, edema formation and ulceration, and in the rapid recanalization of thrombosed superficial varices. It is, therefore, one of the main causes contributing to the number of recurrences following surgical treatment of varicosities.

Since the communicating veins are inconstant in position, and since the commonly used tests are frequently unreliable in determining the existence and location of incompetency in these vessels, the author attempted to attack the problem from another angle, through the use of venography.

A tourniquet was lightly placed around the limb above the level at which it was felt the communicating vein was incompetent, and a radiopaque material was injected into a superficial vein in a retrograde direction. X-rays were taken at appropriate intervals.

It was believed that with such a method a means was available for localization of the position of incompetent communicating veins in the leg with a high degree of accuracy. The method was considered to be more efficient in the thigh than in the leg. It was also felt that by the use of venography, long incisions and tedious dissections could be avoided, surgical treatment made more effective, and the incidence of recurrences due to incompetent communicating veins very much reduced.

ABRAMSON

Kellner, A., Correll, J. W., and Ladd, A. T.: The Influence of Intravenously Administered Surface-Active Agents on the Development of Experimental Atherosclerosis in Rabbits. J. Exper. Med. **93:** 385 (April), 1951.

Rabbits on a high cholesterol diet received in addition repeated intravenous injections of the surface-active agents Tween 80 and Triton A 20. The hyperlipemia which developed was characterized by a great increase in blood cholesterol and equivalent or even greater increase in phospholipids. Much less atherosclerosis was observed in this group than in the control rabbits fed cholesterol alone, who also showed hypercholesterolemia, but a much smaller increase in blood phospholipids. Repeated intravenous injections of Tween 80 did not result in resorption of previously induced atherosclerosis.

Of interest was the finding that atherosclerosis developed in some of the animals on normal diets that had received intravenous injections of Triton A 20. This represents the production in the rabbit on a cholesterol-free diet of atherosclerosis morphologically indistinguishable from that produced by cholesterol feeding.

WAIFE

Croot, H. J.: Ligation of the Aorta and the Use of Cellophane for Abdominal Aneurysm. Brit. J. Surg. **38:** 432 (April), 1951.

The author reviewed the cases in the literature in which ligation of the abdominal aorta was performed in the treatment of aneurysm and added the results obtained in his own patient. On the basis of such data he was able to draw certain conclusions.

Tape was found to be the best material for immediate occlusion, either total or partial; simple proximal ligation at times produced a cure or a reduction in size and pulsation of the aneurysm. Cellophane banding of the aorta, without immediate occlusion, brought about a regression of the lesion in several instances.

The risk of serious impairment of the circulation in the lower limbs was found to be small, provided it was good beforehand. However, if the blood supply was previously impaired, then ligation of the aorta did produce gangrene in several cases.

Despite the risks associated with the operation, it was the author's opinion that surgery should be seriously considered in cases of aneurysms of the abdominal aorta with symptoms. Provided the patient is a suitable candidate for operation, the only observed contraindication is radiologic evidence of severe aortic calcification.

ABRAMSON

MacCarty, C. S., and Cooper, I. S.: Neurologic and Metabolic Effects of Bilateral Ligation of the Anterior Cerebral Arteries in Man. Proc. Staff Meet., Mayo Clin. **26:** 185 (May), 1951.

This report is based on a case in which both anterior cerebral arteries were ligated. During the postoperative period, examination did not disclose

any marked focal neurologic abnormalities, and the patient was lucid and mentally clear on several occasions. There also were periods in which hypotension, stupor and muscular flaccidity were present. Marked electrolyte abnormalities persisted from the fifth postoperative day until the patient died on the fortieth day after ligation of the anterior cerebral arteries. These consisted of hypernatremia, hyperchloremia and hypochloruria. These electrolyte abnormalities appear to have contributed to the death of the patient. The relation of this unusual electrolyte picture to the cerebral lesions in this case is not yet clear.

SIMON

Ecker, A., and Riemenschneider, P.: Deliberate Thrombosis of Intracranial Arterial Aneurysm by Partial Occlusion of the Carotid Artery with Arteriographic Control. Preliminary Report of a Case. J. Neurosurg. **8:** 348 (May), 1951.

The goal in the therapy of intracranial arterial aneurysm by carotid ligation is sufficient impairment of arterial flow to produce thrombosis of the aneurysm alone, without causing cerebral anemia or thrombosis of the artery from which the aneurysm arises.

The case history of a patient with a saccular aneurysm of the internal carotid artery near its bifurcation is presented. Five carotid arteriograms were done on this patient to follow the progress of the therapy. It was possible to position the head so that the aneurysm would assume a dependent position and would fill with Diodrast and the dye would be retained. First, the aneurysm was diagnosed by carotid arteriography. Then it was observed by arteriography before and after one hour of digital carotid compression. No thrombosis occurred in the aneurysm. Finally, a clip was placed on the common carotid artery so as to occlude the vessel partially and the intracarotid mean pressure was diminished 50 per cent. A week later, carotid arteriography showed that 80 per cent of the aneurysm was obliterated. One month later a carotid arteriogram revealed excellent filling of the internal carotid artery and its branches with no definite evidence of residual aneurysm. The parent vessel was intact.

The authors suggest that percutaneous cerebral arteriography should be used to control the therapy of most intracranial aneurysms.

FROBESE

Engel, C.: Syphilis of the Pulmonary Artery. M. J. Australia **1:** 749 (May), 1951.

The author discusses the rarity of syphilitic changes in the pulmonary artery as opposed to the aorta in spite of the fact that both vessels arise from the same anlage of the walls. The difference in the thickness of the two vessels, the number and distribution of the vasa vasorum, the differences in dynamic stresses, as well as differences in chemical factors playing a possible role in this marked dissimilarity in reaction to the same disease are evaluated.

BERNSTEIN

Israels, M. G.: Aneurysm of the Pulmonary Artery. Canad. M. A. J. **64:** 443 (May), 1951.

This is a case report of a large pulmonary artery aneurysm due to arteriosclerosis in a 57 year old white woman. There was a loud systolic murmur over the second left intercostal space. The blood pressure was normal and there was no polycythemia or clubbing. The x-ray suggested lymphoma of the hilar region. On autopsy the aneurysm involved the trunk and two main branches of the pulmonary artery. The right ventricle was considerably hypertrophied, and sections of the lungs revealed marked pulmonary arteriosclerosis with moderate sclerosis of the venules.

WAIFE

Goodwin, J. F., and Kaplan, S.: "Priscol" in Treatment of Peripheral Vascular Disease. Brit. M. J. 4715: 1102 (May 19), 1951.

The authors found that "Priscol" (2-benzyl-4,5-imidazoline hydrochloride) in dosage of 50 to 100 mg. given orally three times a day appeared to be an effective vasodilator in a series of 12 patients with occlusive arteritis, and in two with Raynaud's disease. This therapy was continued for as long as three months. The objective criteria for this study consisted of the fluorescein circulation rate and reflex heating tests. The best results were obtained in those patients in whom vasodilatation of collateral vessels was possible. Limited improvement was noted in those with advanced occlusive disease. In those with mild arterial involvement, this drug gave relief of symptoms and seemed to delay the onset of more severe ischemic change. It was felt that "Priscol" may act as a valuable alternative to sympathectomy in cases unsuited to operation, and in mild cases of arterial disease. It is suggested as an interim therapy in acute occlusive arteritis until the extent of the disease is assessed. The authors feel that because of its low toxicity and its ease of administration, its further trial is warranted.

TANDOWSKY

Torkildsen, A., and Koppang, K.: Notes on the Collateral Cerebral Circulation as Demonstrated by Carotid Angiography. J. Neurosurg. **8:** 269 (May), 1951.

Under usual conditions, blood containing a contrast medium injected through the internal carotid artery on each side passes to the vessels of the homolateral hemisphere and does not go to the opposite hemisphere in any significant amount. However, when one carotid is partially or totally obliterated,

the opposite carotid must compensate if the homolateral hemisphere is to survive cerebral ischemia.

The authors present four cases of carotid obstruction studied with cerebral angiograms in an attempt to demonstrate the collateral cerebral circulation. From these cases, they conclude that blood containing contrast medium from the internal carotid on the good side passes over to the cerebral vessels of the pathologic hemisphere via the circle of Willis. Furthermore, it may flow down the internal carotid in reverse direction until it reaches the obstruction. In cases of bilateral internal carotid obstruction, arterial blood may reach the cerebral hemispheres by way of the basilar artery, as shown by cerebral angiography.

The external carotid-internal carotid communications are listed and described, but it is pointed out that they are small vessels of probably limited importance.

The importance of angiography in the diagnosis of carotid thrombosis is emphasized.

FROBESE

Kobernick, S. D., Moore, J. R., and Wiglesworth, F. W.: Thrombosis of the Renal Veins with Massive Hemorrhagic Infarction of the Kidneys in Childhood. Am. J. Path. **27**: 435 (May–June), 1951.

The authors report four cases of hemorrhagic renal infarction, associated with dehydration resulting from diarrhea and vomiting, in children suffering from nonrenal disease. In such patients, the infarction is secondary to venous thrombosis, the arteries remaining uninvolved.

Clinical observations were few, mainly because of the short survival period. Dehydration following the fever of serious infection (pneumonia, mastoiditis), and diarrhea were common to all four cases. Albuminuria and hemoglobinuria were noted twice. An interesting clinical finding was the palpation of enlarged kidneys, and the authors stress the importance of this in children with sepsis and hemoglobinuria. While the original thrombosis occurs apparently in the small veins at the corticomedullary junction, it eventually involves the large renal veins, sometimes the inferior vena cava, and in most instances the smaller branches of the pulmonary artery. The authors do not describe the process as phlebitis and all bacteriologic studies have been negative. The renal involvement is usually bilateral, consisting of a widespread hemorrhagic necrosis in the cortex and especially the medulla, imparting to the kidneys a mottled dark red, occasionally massive reddish black, appearance.

GOULEY

Petch, C. P., and Camb, M. D.: Cor Pulmonale from Recurrent Pulmonary Embolism. Lancet 6669: 1346 (June), 1951.

The authors report a case of chronic cor pulmonale due to recurrent emboli to the pulmonary artery. Only seven such cases have been previously reported. It is often difficult to distinguish at autopsy between persistent emboli and thrombosis in situ. It seems possible that many of the cases described at necropsy as examples of pulmonary artery thrombosis may actually represent the result of former emboli, since an unexplained or "primary" thrombosis in such a situation is less easy to understand. Some cases diagnosed as Ayerza's syndrome may have a like origin. The reason why these emboli persist while others disappear does not seem to be established. In the present case there seems little doubt that the original obstructions suffered recurrent additions to their substance, and, had the cause of the dyspnea been understood, ligature of the veins would have been an obvious measure. The point to be emphasized is that chronic heart failure does arise in this manner.

BERNSTEIN

Gifford, R. W., Jr., and Hines, E. A., Jr.: Complete Clinical Remission in Thromboangiitis Obliterans during Abstinence from Tobacco: Report of Case. Proc. Staff Meet., Mayo Clin. **26**: 241, (June) 1951.

A case of thromboangiitis obliterans in which a 12 year "clinical cure" was obtained following complete withdrawal of tobacco has been reported and discussed. Whether the beneficial effect of abstinence from tobacco in thromboangiitis obliterans accrues primarily from arresting the disease process in the arteries and veins, or whether circulation is improved merely by relaxation of unaffected arteries is hypothetical. That abstinence from tobacco is beneficial and should form the primary basis for all treatment in these cases is not hypothetic but is a well-established fact.

SIMON

Haft, D. E., and Prior, J. T.: Bilateral Cortical Necrosis of the Kidneys Following Treatment of an Unusual Case of Heart Block. Ann. Int. Med. **34**: 1483 (June), 1951.

An obese nonhypertensive female first developed syncope at the age of 53. At that time the electrocardiogram demonstrated the presence of a 5:1 A-V heart block associated with a right bundle branch block. A spontaneous reversion to normal sinus rhythm occurred shortly afterward but the right bundle branch block persisted. Approximately 18 months afterward, she was admitted to the hospital because of repeated syncopal episodes during the two weeks prior to her hospital admission. During her hospital stay several Stokes-Adams seizures occurred. These were associated with prolonged asystole which responded to intracardiac injections of epinephrine. Between attacks the electrocardiogram demonstrated either complete AV heart block or high degrees of partial heart block. On the

third hospital day, she became semiconscious and oliguria was present. She died on the fourth hospital day, several hours after a recurrent Stokes-Adams seizure. An autopsy was performed and the significant microscopic findings consisted of the following: The interstitial tissue separating adjacent myocardial bundles appeared to be replaced by large amounts of adipose tissue. The structure of the renal cortex was totally disorganized because of bilateral cortical necrosis. The renal complication is interpreted to be a terminal event conceivably due either to the circulatory stasis resulting from the altered hemodynamics during repeated Stokes-Adams seizures, or to interlobular artery constriction induced by the repeated injections of epinephrine. Of the two explanations, the latter is considered to be the more likely.

WENDKOS

Giampalmo, A.: The Arteriovenous Anginomatosis of the Lung with Hypoxaemia. Acta med. Scandinav. Suppl. **251:** 1, 1951.

This report is concerned with the review of 57 cases of pulmonary arteriovenous angiomatosis, including 3 observed by the author. The manifestations of this disease include cyanosis of long duration and increasing severity, dyspnea on effort, clubbing of the fingers, polycythemia with considerable increase in the hematocrit level, increase in the total blood volume, oxygen unsaturation of the arterial blood, hemoptysis and epistaxis, neurologic symptoms including headache, paresthesias, transient dysarthria, vertigo, and epileptiform or syncopal attacks, and thoracoepigastric pains. In many cases there is a hereditofamilial tendency to angiodysplasias. The patients commonly have telangiectasias and angiomas of the skin and mucous membranes. Murmurs which are systolic or continuous, altered by breathing and located over the angioma constitute the major auscultatory evidence of this disorder. Roentgenographic studies disclose rounded or lobulated shadows, usually in the lower lobes and often connected to the hilum by one or more band-shaped shadows. Pulsation of these rounded shadows and volumetric alterations in them may be observed fluoroscopically during the Valsalva or Müller maneuvers. The symptoms are primarily the result of the hypoxemia since a large volume of blood passes through the shunt in the lesser circulation; the blood flows from the branches of the pulmonary artery directly into the left heart through the branches of the pulmonary vein without entering the capillaries of the pulmonary alveolar system. This disease must be differentiated from the congenital cyanotic cardiac disorders, Vaquez's disease, and Arrilaga-Ayerza's disease. Many patients have been relieved of all symptoms by surgical removal of all or part of the lung containing the arteriovenous angioma.

ROSENBAUM

OTHER SUBJECTS

Wilson, E. B., Jr., and Zimmerman, S. L.: Bernheim's Syndrome in the Light of a Fatal Case. Am. J. M. Sc. **220:** 257 (Sept.), 1950.

The authors feel that a diagnosis of Bernheim's syndrome may be made when, in the presence of any etiologic factor which causes a considerable burden on the left ventricle and results in its enlargement, the signs of systemic venous engorgement far outweigh in clinical significance the manifestations of left ventricular failure. When this clinical state can be explained at autopsy by the almost complete obliteration of the right ventricular cavity by an extremely hypertrophied interventricular septum, it is contended that the concept of Bernheim has been fulfilled.

DURANT

Greenberg, L. D., and Rinehart, J. E.: Plasma Cholesterol Levels of Cholesterol Fed Control and Pyridoxine Deficient Monkeys. Proc. Soc. Exper. Biol. & Med. **76:** 580 (March), 1951.

The ad libitum feeding to rhesus monkeys of a low or moderate fat diet containing 1 per cent cholesterol resulted in a greater hypercholesterolemia in the pyridoxine deficient monkey than it did in the control monkey. This occurred despite the fact that the cholesterol intake of the control animal was two to four times greater than that of the deficient animals. Whether this results from enhanced absorption or a decline in the ability of the vitamin B_6 deficient monkey to handle cholesterol is not known.

MINTZ

Azarnoff, E. L., Batty, T. V., Roofe, P. G., and Maffet, M.: A Comparison of the Number of Circulating Blood Cells in Different Parts of the Circulatory System. Science **113:** 363 (March 30), 1951.

Blood was removed from the heart, veins, and periphery of 32 dogs without anesthesia. The authors used silicone-treated needles to prevent clotting and adherence of cells to the needle. Statistical analysis revealed no significant differences between heart, venous and peripheral blood with regard to the total number of erythrocytes or leukocytes per unit volume. The average hematocrit of venous blood was 43.8 per cent and, the hematocrit of heart blood was 42.9 per cent.

WAIFE

AMERICAN HEART ASSOCIATION, INC.

1775 Broadway, New York 19, N. Y.

Telephone Plaza 7-2045

HEART MODELS

Latex models of the human heart to replace the plaster ones previously available will be ready early in April. They will fill a long-felt need for better heart models as a visual aid in undergraduate and postgraduate education. The new models, which will be safer to handle, will also be useful as an aid in the teaching of fluoroscopy. Physicians and professional groups may wish to use them for demonstrating heart conditions to patients and lay groups.

Ten different models have been prepared under the direction of a special committee of the Scientific Council, under the chairmanship of Dr. J. Scott Butterworth. Other members of the Committee are Charles A. R. Connor, M.D., Dickinson W. Richards, Jr., M.D., and Henry Taylor, M.D.

The types represented in the set are: the average normal heart; transverse; vertical; moderate mitral stenosis; marked mitral stenosis; mitral stenosis and aortic regurgitation; aneurysm of the ascending limb of the aortic arch and aortic insufficiency; hypertensive heart and tortuous arteriosclerotic aorta; chronic cor pulmonale; and a cast of the interior of the normal heart representing the actual size of the four chambers.

Each model is set on a base which can be inserted into a rubber model of the human diaphragm.

The models were made by Abram Belski, sculptor at New York Medical College, Department of Anatomy. They may be obtained from the American Heart Association as a set or individually.

A complete set of ten with one display stand will cost $150. Single models with a display stand will cost $22.50, and single models without a display stand $16.50. Packing and shipping costs are extra.

The models are unpainted, but instructions for coloring the arterial and venous sides of the heart will accompany the models. A complete description and photographs will be available shortly.

Inquiries or orders should be sent to: Mr. H. Douglas Chisholm, American Heart Association, 1775 Broadway, New York, N. Y.

INTER-AMERICAN CONGRESS

April 1 is the deadline for submitting summaries of papers for the Fourth Inter-American Cardiological Congress being held in Buenos Aires from September 1 to September 6, 1952. The summaries, not to exceed 200 words, are to be sent to: Fourth Interamerican Cardiological Congress, Larrea 1132, Buenos Aires. If possible, the papers should be written in Spanish or Portuguese, as well as English. Members may send as many papers as they wish, but will be allowed to read only one or two. Time limit allowed to each speaker at the Congress will be 15 minutes, including the exhibition of lantern slides or films.

Titular Members may be accompanied by their relatives, who will be considered as Associate Members. Registration fee will be about $18.00 for Titular Members, and about $7.00 for Associate Members. These fees may be paid upon arrival in Buenos Aires. Applications for registration may be obtained from Congress headquarters at the above address.

The opening session of the Congress will take place on Sunday, August 31. The Congress Dinner is scheduled for September 6 at 9 P.M.

A number of complementary activities are planned during the week of the sessions, including a banquet, a theatrical performance and a trip to the islands of the Parana Delta. During the week of September 7, excursions will be organized.

The Argentine Committee of the Congress will be the official hosts. Dr. Pedro Cossio, Argentine Committee President, will preside. Other officers of the Argentine Committee are

Dr. Eduardo Braun Menendez, Dr. Carlos Rodrigue, Dr. Alberto C. Taquini and Dr. Roberto Vedoya, Vice-Presidents; Dr. Blas Moia, Secretary General; Dr. Juan C. Etcheves, Recording Secretary; and Dr. Jorge Gonzalez Videla, Treasurer.

ANNUAL MEETING SCHEDULE

Following is the schedule of meetings and events for the Association's Annual Meeting and Scientific Sessions to be held at the Hotel Statler in Cleveland, Ohio, April 17–20, 1952. The Scientific Sessions will be held on Friday and Saturday, April 18 and 19, from 9:00 A.M. to 5:00 P.M.

Thursday, April 17

9:30 A.M.
Assembly of the American Heart Association
Panel Discussions
1:00 P.M.
Luncheon for Assembly Members
2:00 P.M.
Reports of Executive Staff
Election of Officers and Directors
Presentation and Discussion of Panel Reports
5:30 P.M.
Executive Committee of Scientific Council

Friday, April 18

9:00 A.M.
Scientific Sessions, including the George E. Brown Memorial Lecture, by Dr. Isaac Starr
10:00 A.M. (Concurrently with Scientific Sessions)
Panel—"Your Heart Association in Action." Open to members of the Assembly and any members of Heart Associations attending the Annual Meeting.
12:00
Annual Meeting of Members
2:00 P.M.
Scientific Sessions
2:00 P.M. (Concurrently with Scientific Sessions)
Panel—"Doctors Meet the Press." Discussion open to same groups as the morning panel.
7:00 P.M.
Annual Dinner, with presentation of Gold Heart Awards

Saturday, April 19

9:00 A.M.
Scientific Sessions, including the Lewis A. Conner Lecture by Dr. Dickinson W. Richards, Jr.
Special Basic Science Sessions will be held concurrently with the General Scientific Sessions
2:00 P.M.
Scientific Sessions

Sunday, April 19

10:00 A.M.
Scientific Council

STAFF CONFERENCE

A staff training conference for personnel of affiliated heart associations will be held April 14 to 16 at the Hotel Hollenden in Cleveland, preceding the Annual Meeting of the AHA. The sessions are being planned by the Staff Conference of Heart Associations, which is composed of executive secretaries and other staff members of heart associations, in cooperation with the AHA national staff. Board and Committee Members of heart associations are invited to attend the staff training conference.

VERMONT HEART ASSOCIATION

The Board of Directors of the Association has approved the application of the Vermont Heart Association for affiliation.